



Conflicts of Interest in Clinical Trial Recruitment & Enrollment: A Call for Increased Oversight

A White Paper

by

The Center for
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& Policy

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On March 23, 2009, the Center for Health & Pharmaceutical Law & Policy at Seton Hall Law School hosted an invitation-only Forum to address the ethical, legal, and policy issues posed by conflicts of interest that could influence investigator judgment in the recruitment and enrollment of research participants. Entitled *Protecting Participants, Advancing Science: An Agenda for Reform of Clinical Research Recruitment and Enrollment*, the Forum brought together leaders from academic medicine and industry, consumer representatives, legal and ethics experts, and government officials. The Center wishes to thank those individuals who participated in the Forum for their time and for the lively, insightful discussion they made possible. Forum participants are identified in Appendix A. The Center would also like to thank Michael D. Alexander of sanofi-aventis, Kenneth A. Getz of the Tufts Center for the Study of Drug Development, Michael F. Murphy of Worldwide Clinical Trials, and Diane Simmons of the Center for Information & Study on Clinical Research Participation, for sharing their time and insights with us during the production of this White Paper.

All views and recommendations contained in this White Paper are solely those of the faculty and researchers of the Center for Health & Pharmaceutical Law & Policy identified on the authorship page. They do not necessarily reflect the perspectives of the Forum participants, the experts with whom we spoke during the research and writing process, other members of Seton Hall Law School's faculty or staff, or members of the Seton Hall Law School Board of Visitors or other Advisory Boards.

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EXECUTIVE SUMMARY

Collaboration among industry, government, and medicine in the pursuit of clinical research is critical to driving scientific progress, particularly as industry increasingly replaces government as the primary source of research funding. However, the compensation methodologies employed by industry, as well as other financial relationships between industry and physicians, create potential conflicts of interest that possibly jeopardize the rights and well-being of research participants as well as the integrity of research results.

While the landscape of clinical research has changed dramatically – the number of trials has increased, industry funds a larger proportion of research, and more research now occurs in physicians’ private offices – federal policy on recruitment and enrollment, and conflicts of interest in research more generally, has not changed substantially.

In this White Paper, we make the following recommendations for reform of public policy and industry practice:

SUMMARY OF RECOMMENDATIONS

General Principles

- The goal for public policy should be to structure physician-investigator payment to achieve financial neutrality between treatment and research, thus ensuring that a physician’s decision to conduct clinical research, as well as his or her decision to recommend that a particular individual participate in a clinical trial, is grounded in reasons unrelated to investigator compensation.
- Public policy in this area should be developed in the first instance through the regulatory process, to facilitate careful identification and discussion of the issues and to facilitate the development of best practice models. Reform through the prosecutorial process leads to an undue focus on outlier cases, lacks transparency, and does not include the voices of all relevant stakeholders.

Compensation for Research

- **Per Capita and Global Payments:** Current federal policy does not provide sufficient guidance about the principles or methodology by which to determine the “fair market value” of a physician-investigator’s services in the clinical research context. Government regulations providing guidance on investigator compensation should seek to achieve financial neutrality as between treatment and research. The fair market value of physician time in the clinical research context should track the fair market value of physician time spent engaged in clinical work. In order to avoid a disincentive for physicians to conduct research, compensation for clinical trial work should include delineated reimbursement for expenses, such as screening interviews or tests and data monitoring and reporting, that do not arise in the clinical context.
- **Finder’s Fees and Bonuses for Recruitment and Retention:** The federal government should bar the following: any payment solely for a referral to a research trial, any payment methodology that conditions payment for expenses attendant to screening potential participants on the individual enrolling in the trial, and all bonuses for recruiting or retaining a certain number of participants. These types of payments create conflicts of interest that

can incentivize investigators to recruit and retain individuals who do not meet the study's inclusion and exclusion criteria or to deemphasize information that might discourage individuals from consenting to trial enrollment.

- **Payment with Equity Interests:** The federal government should also prohibit compensation for research in the form of an equity interest in the sponsor of a clinical trial.

Other Conflicts of Interest in Research

- The current framework for federal policy to oversee investigators' conflicts of interest should be revised to specify certain conflicts that will disqualify a researcher from serving as an investigator. For example, holdings by investigators or their immediate family members that provide a direct interest in the outcome of the research, such as stock or stock options in a privately held company or equity in a publicly traded company above a de minimis amount, should be barred. Compelling circumstances may justify individuals with such interests to perform consulting services on matters related to the trial, but any such cases should be reported to the Food & Drug Administration prior to the trial's commencement. The same policy should also apply to intellectual property interests in a drug, device or other product investigated by the clinical trial.
- Federal regulations should require that all other conflicts of interest, arising from the varied and frequent financial relationships between industry and physicians, be identified and managed.

Enhancing Institutional Oversight of Conflicts of Interest

- Federal regulations should be amended to require the following:
 - At the commencement of research, institutions should evaluate relationships between industry and physician-investigators to determine if the magnitude and form of the individual's financial interest with the sponsor, the longevity of the relationship, or other factors suggest that there is a conflict of interest requiring elimination, reduction, or management.
 - Investigators should be required to report all financial interests, irrespective of amount, to an institutional committee for review, rather than leaving it up to investigators to determine if the interest could reasonably be expected to affect the research. Institutions should also be required to establish internal databases that investigators must update as information changes about their financial relationships with for-profit entities.
 - Individual institutions should have the discretion to determine whether to create a special conflicts of interest committee to review and manage individual investigators' conflicts of interest or whether to delegate those responsibilities to the institutional review board (IRB).
 - For research conducted in academic medical centers, a committee of the board of directors, including members independent of management and the faculty, should oversee institutional conflicts of interest in research. The board committee's oversight should extend beyond the primary institutions, such as the medical school or university, to any not-for-profit institutes or for-profit corporate entities that are substantially controlled by or operate under the auspices of the medical school or university.

Overseeing Conflicts of Interest Outside of Academic Medical Centers

- Review and management of investigator or institutional conflicts of interest prior to the time that research begins should be mandated by regulation and subject to contemporaneous government oversight.
- Federal regulations should charge IRBs with review of conflicts of interest held by investigators and entities conducting research in community settings. Federal regulations should provide clear guidance to IRBs about the nature and scope of information they should review, the standards for the review, and the alternatives for eliminating, minimizing, or managing a conflict, both for investigators and institutions. Federal regulations should also spell out clearly the obligation of community-based physicians acting as investigators or institutions acting on their behalf to report information about compensation for research and other financial interests to IRBs.

Achieving Transparency

- Federal law should require disclosure of payments for conducting clinical trials and other relevant financial interests. Specifically, before research commences, research sponsors should report to the Food & Drug Administration and recipients of federal grants should report to the granting federal agency relevant equity and ownership interests as well as all payments, above a de minimis amount, to the investigator and the investigator's institution or practice group by the company whose product is under review in the clinical trial.

Enhanced Training for Investigators

- Federal regulation should require that training about the nature of conflicts of interest, their potential for harm, and the ways that conflicts can be managed, reduced, or eliminated should be mandatory for all investigators who conduct clinical research within and outside of academic medical centers. For physician-investigators outside of academic medicine, training should also cover key elements of research: the importance of inclusion and exclusion criteria and informed consent, the ethical and scientific issues posed by particular research methods such as double blind placebo-controlled studies, and their obligations as an investigator as compared with those of a treating physician.

INTRODUCTION

The collaboration between industry and medicine in the arena of clinical research is critical to driving scientific progress. This collaboration leads to the production of drugs and devices to prevent, diagnose, and cure illness, as well as innovations that prolong the lives and improve the quality of life of seriously ill patients. Investigators, both inside and outside of academic medical centers, depend on industry funds to advance clinical research to break new barriers in patient care. This reliance on industry to fund research and innovation has brought with it increasing financial ties between drug and device companies and the physicians and institutions who conduct research.

Recent media coverage, government reports, and the academic literature have highlighted the pervasive nature of conflicts of interest between medicine and industry in treatment, medical education, and scientific publication.¹ Congressional investigations, government prosecutions, and press reports revealing the nature and extent of these conflicts have led to calls for reform.² Most recently, congressional inquiries have focused on “ghostwriting,” the preparation of articles on research findings undertaken by industry, and attributed to scholars paid to lend their names to the reported results.³ Reform measures and proposals have focused on greater transparency in the financial relationships between pharmaceutical and medical device companies on the one hand and physicians and health care facilities on the other.⁴ State legislatures have taken the lead in barring certain activities that create conflicts, such as gifts, meals, and other financial benefits for physicians.⁵ However, substantial conflicts in clinical research remain unaddressed.

This White Paper focuses on conflicts of interest in the research context; specifically those that potentially affect physicians in their roles as investigators overseeing clinical trials. Conflicts of interest in this context have the potential to affect the rights and interests of those who volunteer to participate in clinical trials. When investigators have financial interests in the outcome of the research or stand to gain substantially from conducting a clinical trial, it may affect their judgment throughout the conduct of the trial, including the many judgments that must be made during the process of enrolling and recruiting individuals to participate as research subjects. Potential participants can be harmed by recruitment practices that insufficiently inform them of the risks of the study, ignore medical conditions that place them at risk in the trial, or encourage them to discontinue or forego a treatment regimen likely to be better for them than the regimen being evaluated in the trial. Manufacturers have also conducted studies as a way of introducing physicians to their products and obtaining the physicians’ brand loyalty, rather than as a genuine scientific inquiry.⁶ Even if enrollees are not physically harmed in these studies, they are asked to participate in research that is a sham, violating the trust they have placed in the researchers who recruited them. Such studies undermine the integrity of the research enterprise; public revelation of the studies is likely to diminish willingness to participate in research.

Moreover, the scientific integrity and validity of the research results may be impaired whenever a financial conflict influences the judgment of physician-researchers in the recruitment and enrollment process. Each clinical trial has a protocol that enumerates the eligibility criteria for trial participation. If physicians recruit individuals who do not meet a study’s inclusion and exclusion criteria, for example because their disease is not of the severity specified in the study protocol or because they take certain medications the protocol prohibits, the resultant study data may not be valid.

The emphasis of this White Paper is on the conflicts of interest that arise when physician-investigators or the institutions under whose auspices clinical trials are conducted have a financial incentive to enroll individuals in clinical research or a financial relationship with the trial sponsor that potentially threatens the objectivity of their decisions regarding the pursuit of such research. We also recognize the negative consequences that may exist when compensation for research is so inadequate that it discourages physicians and institutions from conducting research at all. A recent *New York Times* article reported that the “great majority” of oncologists decline to participate in clinical trials because “[t]hey make little or nothing on trials and, in fact, often lose money.”⁷ Clearly, financial incentives and disincentives alike have the potential to influence physicians’ judgment in the recruitment and enrollment process.⁸

In analyzing investigator over-compensation, we address both the specific reimbursement for a particular trial as well as, in some contexts, the totality of the physician’s financial relationship with the trial sponsor. This White Paper argues that the goal for public policy should be to structure physician-investigator payment to achieve financial neutrality between treatment and research. This approach would ensure that a physician’s decision to conduct clinical research, as well as his or her decision to recommend that a particular patient participate in a clinical trial, is grounded in reasons unrelated to investigator compensation.

Evolving market realities underscore the importance of public policies to address conflicts of interest, especially as they relate to enrollment and recruitment. Pressures to develop health care products, obtain government approval, and bring them to market as quickly as possible have increased in recent years. This pressure extends to testing new products and the need to recruit and enroll more participants into research. These market forces are likely to intensify as patents for blockbuster drugs expire, drug pipelines dwindle, and companies face the current economic downturn. Potential health care and patent reform create additional uncertainties for drug and device makers.

The number of clinical trials in the United States has climbed dramatically in recent years. Between 2000 and 2006, clinical trials increased from 40,000 to 59,000 – a nearly 50 percent jump.⁹ At the same time, the Food & Drug Administration’s (FDA) heightened attention to ensuring that products are safe before granting marketing approval has led to more trials in each development phase, to more participants in each trial, and to increasingly complicated protocols, all of which heighten recruitment hurdles.¹⁰ Nearly a third of clinical trial time – more than any other clinical trial activity – is spent recruiting participants.¹¹ Moreover, recruitment and enrollment problems lead to nearly half of all clinical trial delays, with more than 70% of clinical trials delayed from one to six months.¹² These delays increase drug and device companies’ out-of-pocket expenses and run down the clock on the period during which companies can earn government-protected monopoly profits for sale of the products being studied.

The current economic climate presents additional challenges for policymakers concerned with protecting the rights and interests of prospective research participants throughout the recruitment and enrollment process. Illness, economic circumstances, and other situational factors can create or exacerbate vulnerabilities of research participants. Individuals living in poverty or without health insurance are disproportionately likely to participate in clinical research.¹³ Under-employment and loss of health insurance make clinical trials appealing to some potential participants who otherwise would not consider enrolling but are attracted by the promise of payment or free health care attendant to the trial. Recent media reports reveal that growing numbers of healthy individuals are turning to Phase I trials (in which drugs are tested in humans for the first time) to earn money;¹⁴ this type of trial attracts primarily low-income

minority men.¹⁵ Even before the economic downturn, press reports noted that some lower socio-economic class individuals, often immigrants, rely on clinical research as their primary source of income.¹⁶ The ranks of clinical trial participants also include many individuals, predominantly uninsured white women, who choose to participate in Phase II or III trials in part to obtain health care.¹⁷

The clinical trial system necessarily relies on the physician-investigators who conduct research to serve as trustworthy gatekeepers, protecting both the integrity of the research as well as the health and welfare of the individuals upon whom the experimental products are being tested. However, as the drug and device industry has funded a growing share of clinical research, physician-investigators are increasingly the recipients of financial incentives creating conflicts that may undermine their ability to serve in this role. Before 1980, the National Institutes of Health (NIH) funded most medical research.¹⁸ In the 1980s, however, NIH funding fell and drug industry funding rose six-fold.¹⁹ Today, drug and medical device companies fund up to 80% to 90% of all clinical trials; in 2005, industry invested 78% more in research and development than did the federal government.²⁰ Although the American Recovery and Reinvestment Act allotted \$8.2 billion dollars to the NIH for research,²¹ this stimulus funding is a one-time infusion of money, and is slated to end in September 2010. As a result, industry will continue to serve as the primary source of funding for clinical research.

As funding for clinical research has shifted, its locus has as well. In addition to academic medical centers, research is now conducted in community hospitals, doctors' offices, and research institutes.²² By 2004, nearly 75% of the clinical research sites sponsored by industry were physicians in private practice or for-profit research centers.²³ Between 1994 and 2004, academic medical centers fell from 63% to 26% of sites where clinical research is conducted.²⁴ The shift away from academic medical centers creates several distinct concerns about financial conflicts of interest, primarily because when physicians in private practice conduct industry-funded research, they may profit directly and personally from recruiting, enrolling, and retaining patients in research.²⁵ Community-based physician-investigators also generally have less training and experience conducting clinical trials than those in academic medicine.²⁶ In addition, community-based physicians are likely to recruit their own patients to participate in clinical trials.²⁷ Combined with the high level of trust patients place in their personal physicians,²⁸ this heightens the risk that prospective participants might agree to enroll in a trial without making an independent evaluation of its risks and benefits. The phenomenon of the therapeutic misconception may also arise, whereby research participants do not understand the distinction between treatment – proposed or provided by their physician solely for their benefit – and research, which may provide clinical benefits for participants in some trials, but is not designed primarily to serve their interests.²⁹

Physician-investigators at academic medical centers are also subject to conflicts of interest that may affect recruitment and enrollment decisions. Physicians in academia face institutional pressure to secure research funding to support their salaries, and their salaries may vary depending upon the amount of funding they obtain. They also have other incentives to conduct research, including publication of the results in the medical literature, a requirement for tenure and promotion.³⁰

Civil lawsuits, government investigations and prosecutions, and news investigations have shed light on conflicts of interest that may have adversely affected recruitment and enrollment or the actual conduct of clinical trials, and, more tragically, possibly placed participants at serious risk of harm. In one well-known case, 18-year old Jesse Gelsinger died while participating

in a Phase I gene therapy trial.³¹ Jesse Gelsinger's father sued the researchers, the hospitals that employed the researchers, the university that approved and sponsored the trial and employed a bench scientist involved with the trial, and a bioethicist who consulted on the trial's design.³² Among other claims, Jesse's father asserted that the researchers committed fraud, based in part on the fact that neither the researchers nor the informed consent document told Jesse or his father that the study's co-principal investigators and the university institute conducting the research had a substantial equity stake in the vector used in the clinical trial.³³

In 2006, Katrina McKenzie, a participant in a clinical trial of ceramic-on-ceramic hip implants, brought a suit against her surgeon and the hospital where the implant surgery occurred.³⁴ The implants in both of McKenzie's hips failed, requiring her to undergo additional surgeries. McKenzie's surgeon testified in a deposition that he received no direct financial benefit from the implant trial because the payments from the device maker which sponsored the trial went to the academic medical center which employed him. McKenzie's surgeon conceded, however, that the trial sponsor did pay him between \$20,000 and \$50,000 a year for consulting work – income that he had not disclosed to McKenzie. In an article in the *Philadelphia Inquirer*, McKenzie's lawyer asserted that the surgeon had a conflict of interest which may have influenced his decision to use the experimental hip implants in McKenzie's case. McKenzie's surgeon denied any negligence. The case settled in August 2008 on the eve of trial.³⁵

A 1999 *New York Times* investigation highlighted the case of Thomas Parham, who enrolled in a clinical trial of a prostate drug at his doctor's encouragement.³⁶ Parham had previously been hospitalized for a chronic slow heart rate, and the clinical trial's protocol specifically excluded patients with that condition from participating in the study. Parham's physician did not inform Parham that the physician was paid \$1,610 for each patient enrolled, an amount that covered study expenses and allowed for a profit for the physician and his associates. Parham's physician informed the drug company sponsoring the trial about Parham's slow heart rate but failed to tell the company about his prior hospitalization. Soon after joining the study, Parham complained of fatigue, a symptom of a slow heart rate, but his doctor dismissed his complaints. Within weeks Parham was hospitalized and given a pacemaker.³⁷

Pharmaceutical companies have also faced government investigation and civil litigation for conducting so-called "seeding studies" designed primarily to market a product to physicians but presented as research to the physicians and the patients they recruit – a practice that stands to undermine the research enterprise as a whole. One such study enrolled 5,557 individuals in a head to head clinical trial of Vioxx and naproxen, with the stated purpose of evaluating Vioxx's gastrointestinal tolerability.³⁸ In fact, a review of company documents made public as a result of litigation revealed that the manufacturer's marketing department designed the study to expose unwitting primary care physicians recruited as study investigators to Vioxx in the months before and after its launch.³⁹ An internal memorandum explained that the trial design focused on demonstrating the advantages of Vioxx to primary care physicians because they were important prescribers.⁴⁰ The patients who participated were not told of the trial's marketing aims, undermining the validity of their consent.⁴¹

Recently, in another example of "research" misconduct, a government investigation into clinical research at Walter Reed Army Medical Center revealed that a principal investigator who had systematically falsified research findings had been paid thousands of dollars for consulting work by the corporation that produced the bone growth product under study.⁴² The researcher's subsequent research at Washington University was suspended when the school learned of the physician's undisclosed conflicts of interest.

The problems represented by these anecdotal cases require a more pervasive public policy response than can be accomplished through private litigation, prosecutions, and newspaper reports. At present, however, the government provides little guidance or oversight of compensation for clinical research, or other conflicts that arise from the financial relationships between industry and investigators and institutions. Federal regulations and guidance statements assign to institutional review boards (IRBs) full responsibility to conduct an ethics review of clinical trials involving human subjects, including proposed recruitment and enrollment practices. Yet IRBs have not traditionally been charged to identify and manage conflicts of interest. Rather, government agencies and professional organizations such as the Association of American Medical Colleges (AAMC) and the Association of American Universities (AAU) recommend that academic medical centers establish standing conflict of interest committees to review and manage conflicts of interest.⁴³ These recommendations, however, are not binding on academic medical centers or other institutions.

Institutions that receive federal government funding for medical research, primarily medical schools and affiliated hospitals, must establish conflict of interest policies, identify the financial interests of investigators, determine if they constitute a conflict of interest, and if they do, decide how to manage or minimize the conflict.⁴⁴ Even where required, conflict of interest policies and practices vary substantially from institution to institution. Moreover, recent research focused on academic medical centers has revealed that institutional practices diverge with some frequency from written policies.⁴⁵ Most community hospitals do not have conflict of interest committees. Rather, the institutions' IRBs are often tasked with reviewing investigators' financial relationships, although it can be difficult for them to gain information about such relationships or disapprove of protocols where a conflict of interest exists.⁴⁶

Beyond the hospital setting, neither physician offices nor many other organizations in the community that conduct research have IRBs. Consequently, as research has extended beyond the walls of the academic medical center, a system of independent (for-profit) IRBs has developed to facilitate these institutions' compliance with federal review requirements.⁴⁷ These independent IRBs review and approve the recruitment and enrollment plan as well as the ethical issues posed by the proposed study to protect the interests of participants and affirm the scientific integrity of the research.⁴⁸ Physicians and private research institutes are not required to provide information to the independent IRB about incentives paid to physicians or others to recruit and enroll patients, overall compensation for the clinical trial, or other relevant financial interests held by the investigator or entity. To the contrary, this information is often considered proprietary, and is therefore frequently not provided to the IRBs charged to evaluate and approve the research protocol.

In sum, while the landscape of clinical research has changed dramatically – the number of trials has increased and research is now largely funded by industry and conducted outside of the academic purview – federal policy on recruitment and enrollment, and conflicts of interest in research more generally, has not changed substantially. Given the mounting pressures to recruit and enroll patients and the current lack of government oversight, policy and practice regarding conflicts of interest in clinical research recruitment and enrollment cry out for reform.

Seton Hall Law's Center for Health & Pharmaceutical Law & Policy held a forum on March 23, 2009 to examine current policy and practice and devise recommendations for change. This White Paper focuses on the need for policy and institutional reform to protect potential research participants and the integrity of research in the recruitment and enrollment process.

CURRENT PRACTICES IN CLINICAL RESEARCH

The drug, device, and biotechnology industries currently fund the majority of clinical trials across a range of settings including academic medical centers, community hospitals, physician practices, and research centers and institutes. The government also funds extramural research, primarily in the academic setting. Conflicts of interest can arise for investigators and institutions due to the compensation methodologies for research as well as the broad array of other financial relationships between industry and physicians or their employers.

A. Definition of Conflict of Interest

In its recent report, *Conflict of Interest in Medical Research, Education, and Practice*, the Institute of Medicine (IOM) defined “conflict of interest” as “a set of circumstances that creates a risk that professional judgment or actions regarding a primary interest will be unduly influenced by a secondary interest.”⁴⁹ Physician-investigators in clinical research have several primary obligations: i) promoting and protecting the scientific integrity of the research; ii) protecting the well-being of participants; and iii) contributing to scientific advances.⁵⁰ In addition, investigators may have a host of secondary interests motivating their participation in research, such as earning the respect of colleagues, supplementing their income, or advancing their career. Importantly, there is nothing inherently wrong with these secondary influences. The term “conflict of interest” does not equate to compromised judgment or action but to the risk of such compromise.

This White Paper focuses on secondary interests that are financial in nature. As explained by the IOM in its report, financial interests may be no more likely to unduly influence an investigator than other secondary interests but, because they are more easily measured, they can be managed through broad-based reform of policy and practice.

B. Compensation for Research

1. *Per-Capita Payments*

Under the most common compensation arrangement, the sponsoring company pays investigators or the institutions that employ them a fixed amount per research participant enrolled.⁵¹ This amount can encompass payment for clinical procedures, physician time, facility use, laboratory costs, pharmacy fees, research coordinator or nurse salaries, and overhead costs.⁵² Also covered are the time spent and costs incurred on nontreatment trial activities such as participant recruitment, the informed consent process, randomization of study medication, adverse events reporting, data management and analysis, audits and communications with the sponsor, and post study follow-up and meetings.⁵³ A study estimating the clinical and nonclinical hours and costs associated with conducting a Phase III oncology trial concluded that the time spent on nontreatment activities was “considerable, and the associated costs are substantial.”⁵⁴ Typically, sponsors have schedules of standard fees for the procedures required by clinical trial protocols; investigators and their institutions have their own schedules, and the two parties negotiate the payment for the trial.⁵⁵

Under legal standards set by federal and state laws barring remuneration for referring patients into treatment, compensation for treatment or services paid for by government must not exceed “fair market value.”⁵⁶ These rules were not developed with clinical research in mind. Nonetheless, they underlie federal law on research compensation; the concept of fair market value drives both industry analysis and enforcement oversight.

Because federal law provides little guidance about how reasonable or fair market value compensation should be determined, or even how to define what the “market” is, companies and the consultants upon whom they rely have developed their own methodologies. A range of methods to set compensation for clinical research has emerged, including: (i) a company’s own past practice; (ii) compensation surveys; (iii) the use of independent third parties to conduct fair market value assessments; (iv) benchmarks such as the Medicare reimbursement rate for a given procedure; and (v) a combination of these methods or other methods altogether.⁵⁷ Inconsistencies abound.

While per capita payments are relatively uncontroversial within industry and the medical profession, they are not unproblematic. Whenever a physician-investigator is paid more for conducting research than for treating patients, he or she has a financial incentive to enroll patients in research, and a potential conflict of interest arises.⁵⁸ Further, some evidence suggests that industry pays physician-investigators more for their services than the government or private insurance companies. A 2002 article in *JAMA* reported that manufacturers offered investigators two to five times the compensation paid by NIH, and that manufacturers paid fees several-fold greater than those of Medicare or third-party carriers.⁵⁹ A Kaiser Permanente health care economist makes a similar claim, stating that study sponsors frequently pay top-of-the-market rates that serve as a source of profit for research sites.⁶⁰ Other experts contest these claims, pointing to evidence that payments for clinical research have remained stagnant as clinical trial protocols have grown increasingly complex, leading to a decline in the number of physicians willing to undertake clinical research.⁶¹

2. Global Payments

The government typically pays research institutions a “global payment” to compensate them for all work on a clinical trial protocol as well as overhead costs. The institution budgets for the work of the investigator and other of its employees by multiplying the percentage of time employees will spend on the project by their respective salaries. While the institution factors into the global payment the number of participants it anticipates will need to be *recruited* to conduct the trial, there is no one-to-one correlation between the number of patients *enrolled* and the amount of the payment.

Drug, device, and biotechnology companies do not typically use global payments, although they do compensate investigators or their institutions for certain fixed expenses which can include a startup fee for work conducted in advance of enrollment. A review of over 237,000 industry-investigator contracts worldwide revealed that over half of the contracts for clinical research in the United States included a startup fee to cover expenses for activities such as agreement processing, protocol review, and preparing the IRB submission.⁶² Paying for expenses such as these separately rather than folding them into a per capita fee makes the budgeting process and clinical trial agreement more transparent. This approach could also reduce the conflict of interest caused by high per capita payments. In addition, it allows for reimbursement of recruitment expenses to investigators even when they do not succeed in actually enrolling participants into the trial. Reimbursement for this legitimate cost of research may reduce the incentive to enroll unqualified candidates to cover expenses.

3. Payment in the Form of Equity in the Sponsor

Some trial sponsors remunerate investigators with company stock or stock options. According to New Jersey’s Attorney General, compensation with stock for clinical research is a “widespread industry practice.”⁶³ Compensation with equity in the sponsor creates a

conflict of interest for physician-investigators because it gives them a stake in the outcome of the research. If the data from the trial are positive, it will boost the sponsor's bottom line, which will in turn increase the investigator's gain through increased stock value and the potential for higher dividend payments.

Remunerating researchers with sponsor stock has been sharply criticized. In a press release announcing the 2009 settlement with device maker Synthes, New Jersey's Attorney General asserted that payment with stock or stock options is "outrageous" and "unacceptable."⁶⁴ The settlement bans compensation of investigators and research institutions with Synthes stock or stock options.⁶⁵ In its "Principles on Conduct of Clinical Trials," PhRMA, the trade organization which represents pharmaceutical and some biotechnology companies, also states that companies should not compensate investigators with stock or stock options.⁶⁶ In contrast, the Code of Ethics on Interactions with Healthcare Professionals promulgated by AdvaMed, the trade group which represents medical device companies, appears to permit all forms of compensation as long as they do not constitute a kickback under federal law.⁶⁷

4. Recruitment and Retention Bonuses

In some trials, payment by industry sponsors also includes bonuses for attaining enumerated recruitment and retention goals.⁶⁸ Bonuses can be paid for securing IRB approval in a timely fashion or for meeting enrollment deadlines. In some instances, companies pay investigators bonuses for exceeding enrollment targets or when research participants complete the study or study milestones. Recruitment incentives can also take the form of a bonus or increase in the per-participant payment after a specified number of participants have been enrolled. Finally, companies may establish a structure in which research sites compete with one another to recruit a sufficient number of participants; those that meet the quota may be allowed to recruit additional participants while those that do not may be dropped from the study.⁶⁹ A 2003 survey study revealed that 74% of research sites were compensated by one or more "competitive enrollment practices"; 78% of these sites received bonuses for on-time participant enrollment and 68% received additional bonuses for over-enrollment.⁷⁰

These bonus payments could influence investigators' decisions about prospective participants' initial or continuing eligibility, thereby potentially placing enrollees at risk or undermining the scientific integrity of the study. In a report on clinical research involving children, the IOM opined that recruitment bonuses are unethical and should be prohibited.⁷¹ The PhRMA Clinical Trials Principles do not explicitly prohibit recruitment bonuses but implicitly discourage them, providing that in cases where enrollment is challenging, payments can be made to compensate for the additional time and effort the investigator or institution must expend on recruitment.⁷² In addition, some companies, such as Pfizer, have adopted policies that explicitly prohibit all incentives "designed to reward the achievement of subject enrollment goals within a specified time frame."⁷³

5. Finder's Fees

A sponsor may also offer a so-called "finder's fee," a payment made to individuals other than the investigator, including other physicians, nurses, medical students, or participants in the clinical trial, for identifying and referring potential study participants.⁷⁴ Definitions of finder's fees vary. As used here, finder's fee refers to payments solely for referrals, not payment for services provided at fair market value as part of the recruitment process, such as the time and effort involved in screening prospective participants to determine if they are suitable candidates or explaining the study to them.⁷⁵

Professional organizations including the American College of Physicians and the American Medical Association (AMA) have rejected the use of finder's fees as unethical.⁷⁶ Many academic medical centers prohibit or sharply limit their use;⁷⁷ some pharmaceutical companies refuse to pay such fees as well.⁷⁸ Moreover, finder's fees may constitute a kickback under federal and state laws.⁷⁹ Still, a recent study suggests that finder's fees may be common. A 2006 survey of 300 clinical research coordinators in academic medicine, community hospitals, physician-based practices, stand-alone research centers, and elsewhere revealed that nearly a third (32.1%) of the coordinators had worked on studies in which finder's fees were paid.⁸⁰

6. Salary

Compensation of physician-investigators in the form of a salary does not in itself create a financial conflict of interest with the potential to affect recruitment and enrollment. Some physicians are employees, for example, of academic medical centers or private physician practices, and draw a salary that may or may not be related to productivity goals. Of course, the absence of a direct financial incentive to enroll research participants does not mean that salaried investigators are without conflicts. Their job security, eligibility for tenure and promotion, and ability to secure government grants and other funding in the future may all depend on their ability to enroll enough participants to conduct research and publish the findings.

7. Other Financial Ties between Industry and Investigators and Institutions

In addition to the compensation they receive for conducting clinical trials, investigators may have an array of other financial ties to drug, device, and biotechnology companies.⁸¹ Industry pays physicians for a broad range of activities, including service on marketing and medical advisory boards, consulting work, and promotional speaking. Traditionally, sales representatives have plied doctors with gifts, meals, and other perks, but these are gradually disappearing. One large national survey of physicians in six specialties found that 94% of physicians reported some type of financial relationship with industry, ranging from receipt of food in the work place (83%) and drug samples (78%) to payments for lectures, consulting, and clinical trial work (28%).⁸² An earlier study found that 43% of scientists in the 50 most research-intensive universities received research-related gifts from industry such as biomaterials or research equipment, trips to professional meetings, and discretionary funds.⁸³ Physicians also participate in the development of new drugs and devices and may own intellectual property as a result, including patents, licenses, and royalty rights.⁸⁴ In addition, physicians may own stock or other equity in drug and device companies, including companies they have founded to commercialize their research findings, and may serve on company boards of directors or as officers.

Like investigators, research institutions can have financial ties to industry that give rise to conflicts of interest. The AAMC defines an institutional conflict of interest as a situation in which "the financial interests of the institution, or of an institutional official acting within his or her authority on behalf of the institution, might affect – or reasonably appear to affect – institutional processes for the conduct, review, or oversight of human subjects research."⁸⁵ Examples of institutional relationships with industry include investments by the institution or its high-level officials in drug, device, or biotechnology companies, industry donations to support endowed professorships or new construction, and industry grants for continuing medical education programs. Relationships such as these are not rare. A survey of medical schools and teaching hospitals revealed that 60% of department chairs had financial relationships with

industry and 67% of departments had received industry support, including receipt of research equipment, funding for continuing medical education or resident and fellowship training, and unrestricted funds.⁸⁶ As one notable example, in 2005 the *Wall Street Journal* reported that the Cleveland Clinic had established and invested in a venture capital fund which had a 4.1% stake, valued at about \$7 million, in AtriCure, a startup company that manufactured a device used off-label in heart surgery.⁸⁷ The chief executive officer of the Clinic sat on AtriCure's Board of Directors and invested in and helped manage the venture capital fund. At the time of the news reports, researchers at the Cleveland Clinic were conducting clinical trials of the AtriCure device; they also endorsed its use in heart surgery at conferences and in journal articles.

Some financial ties pose more risk of unduly influencing recruitment and enrollment practices than others. For example, the IOM has recommended that investigators with a "significant financial interest in an existing or potential product or a company that could be affected by the outcome" of a clinical trial not be permitted to conduct the research unless their participation is justified by compelling circumstances and is effectively managed by the institution, while PhRMA's Clinical Trials Principles provide that "[c]linical investigators or their immediate family should not have a direct ownership interest in the specific pharmaceutical product being studied."⁸⁸ These recommendations reflect a judgment that when investigators have a financial interest in the outcome of a trial it generates an unacceptable risk that their financial holdings may influence decisions about recruitment and enrollment, participant safety, data integrity, and other aspects of the research. The AAMC has opined similarly with regard to institutional conflicts of interest, setting forth a list of financial relationships between industry and institutions which create a rebuttable presumption against conducting research at or under the auspices of the institution.⁸⁹

C. Institutional Oversight of Payment Practices and Other Conflicts of Interest

1. Academic Medicine

In successive reports issued in 2001 and 2002, the AAMC recommended that academic medical centers adopt practices to manage individual and institutional conflicts of interest, including the creation of a conflicts of interest committee to gather information about significant financial interests in research, identify those that are conflicts, and determine steps to minimize or eliminate the conflict.⁹⁰ The AAMC also recommended that conflicts committees appoint a liaison to the IRB and that they report their findings to the IRB before the IRB approves the research in question so that the conflicts committee's determinations can inform the IRB's review of the research protocol.⁹¹ Notably, the AAMC's definition of "significant financial interests in research" excludes "[p]ayments to the institution, or via the institution to the individual, that are directly related to reasonable costs incurred in the conduct of research as specified in the research agreement(s) between the sponsor and the institution."⁹² No provision is made for review of such payments.

Few question that IRBs should receive information about researchers' conflicts and the conflicts committee's proposed resolution of those conflicts.⁹³ However, disagreement exists about how to resolve contrary recommendations emerging from the IRB and conflicts committees.⁹⁴ There is also disagreement about whether IRBs should manage conflicts in the first instance, rather than establishing a separate conflicts committee.⁹⁵ Currently, IRBs are not directly charged with conflict review and management and may lack the necessary expertise, time, and resources. A recent survey of IRB members and chairs in academic medicine

revealed that two-thirds believed that IRBs should weigh investigators' relationships with industry as part of the IRBs' review of the research protocol, regardless of whether the conflicts committee deemed the relationship a conflict of interest.⁹⁶ Less than half of those surveyed reported that their IRB always reviewed industry relationships, however. Reasons for not conducting a review included "that the topic didn't come up (41.8%), they didn't feel it was the IRB's responsibility (20.0%), it was difficult to obtain the information (19.7%), or the IRB lacked the expertise to make an informed decision (11.6%)."⁹⁷ Notably, IRBs have had only limited success managing their own members' conflicts of interest.⁹⁸

In a 2008 report evaluating the progress made by academic medical centers in implementing the AAMC and AAU conflicts management proposals, a joint AAMC and AAU advisory committee concluded that institutions took the proposals seriously, especially those addressing individual conflicts, and attempted to implement them, but had fallen short.⁹⁹ A 2004 AAMC survey revealed that over three quarters of the responding medical schools had created standing conflicts committees but that over a third had failed to establish a rebuttable presumption against participation in research by researchers with a financial stake in the outcome.¹⁰⁰ In addition, only a low fraction of the respondents reported that the conflicts committee had completed its work prior to the IRB's review and approval of the study at issue.¹⁰¹

Academic medical centers have found managing institutional conflicts to be even more challenging than managing individual conflicts. Recently published survey data indicates that only 30 of 125 responding medical centers had an institutional conflict of interest policy and that only 25 institutions reported institutional conflicts to the IRB charged with conducting an ethics review of proposed clinical trials.¹⁰² Anecdotal evidence also supports the conclusion that institutional oversight of both individual and institutional conflicts of interest is uneven. Congressional investigations have revealed that several prominent investigators at academic medical centers failed to report their industry relationships to their universities.¹⁰³

2. Research in Physician Practices, Community Hospitals, and Independent Research Institutes

Even less oversight of conflicts of interest exists outside of academic medicine. Conflicts committees are rare or nonexistent. Some IRBs review physician-investigator's financial relationships with the study sponsor, including compensation to the physician-investigator, but some do not.¹⁰⁴

FDA regulations require investigators to provide the sponsoring company with information about their financial interests; sponsors must collect the information and ensure that conflicts are managed to protect the integrity of the data collected.¹⁰⁵ Sponsoring companies may delegate this (and other) responsibilities to subcontractors called clinical or contract research organizations (CROs).¹⁰⁶ There are also subcontractors that assume investigators' duties, called site management organizations (SMOs); unlike CROs, they are not specifically authorized by regulation. Unless and until the clinical trial results are submitted to the FDA as part of a marketing application, there is little or no review or oversight of conflicts reporting and management by investigators, SMOs, sponsors, and CROs.

When research is conducted outside of academic medicine, the federally-mandated ethics review is most typically performed by an independent IRB.¹⁰⁷ Independent IRBs are for-profit companies unaffiliated with industry sponsors or CROs. They are widely believed to be more efficient than academic medical centers' IRBs, but the quality and objectivity of independent IRBs varies; investigators, SMOs, sponsors, or CROs retain the IRB and have discretion as to

which IRB they choose to hire for each protocol reviewed.¹⁰⁸ IRB accreditation exists but it is voluntary and only a handful of independent IRBs are accredited.¹⁰⁹

Research conducted outside of academic medicine but within general acute care or community hospitals may be reviewed by an in-house IRB, which may also assume jurisdiction over conflicts of interest. A recent study of such hospitals found that 90% had policies and procedures in place requiring IRB review of the financial relationships between physician-investigators and research sponsors.¹¹⁰ However, the study also reported that most of the hospitals that reviewed per capita payments rarely rejected a research proposal for excessive payments due to the difficulty they faced in assessing reasonable or fair market value for the payments to investigators.¹¹¹ The study also found that many physicians who practice in community hospitals are not typically paid by the hospital and may be reluctant to divulge their personal financial information to the hospitals' IRBs. This problem also arises when research is conducted in physician offices and group practices; community-based physician-investigators are under no obligation to disclose their financial information to the independent IRB reviewing the study.

3. Self-Regulation by Investigators

The Public Health Service (PHS) requires that institutions inform investigators about its conflict of interest regulations, the institution's conflict of interest policy, and the investigator's reporting responsibilities.¹¹² The FDA's regulations lack a comparable requirement, requiring only that investigators provide study sponsors with accurate, updated financial information (including any financial arrangements between the sponsor and the clinical investigator, significant payments of other sorts from the sponsor of the covered study, proprietary interests in the tested product, and significant equity interest in the sponsor).¹¹³ The AAMC's 2004 study on implementation of its conflict of interest recommendations revealed that just half of the responding schools provided training on conflicts of interest.¹¹⁴ The lack of training for investigators is problematic because studies show that many physicians do not appreciate the risks posed by conflicts of interest, believing that industry compensation relationships might unduly influence their colleagues but not themselves.¹¹⁵

Physicians are not of one mind about whether conflicts of interest adversely affect their judgment. This ambivalence is reflected in the recent vote by the AMA to reject a proposal that the organization advise its members that it was ethically preferable for continuing medical education not to be funded by industry.¹¹⁶ A chartering of a new advocacy organization, the Association for Clinical Researchers and Educators (ACRE), which seeks to advance collaboration with industry and its counterparts, further evidences the profession's divide.¹¹⁷ ACRE decries "restrictive conflict of interest policies that often sever productive relationships between industry and physicians involved in clinical research and educational outreach."¹¹⁸ Physicians in the community may be even less prepared than investigators in academic medicine to identify and address their own conflicts of interest. Like their counterparts in academic medicine, they do not receive training in conflicts of interest. Moreover, community physicians are less likely to have the knowledge and experience to conduct an independent review of the scientific merits of the trial protocol or of the ethical issues it might pose.¹¹⁹ Often, they regard ethical issues that arise as the sponsor's responsibility and may have a poor understanding of how decisions they make in the recruitment and enrollment process could affect participants' interests and the integrity of the study findings.¹²⁰

GOVERNMENT REGULATION AND OVERSIGHT

A. Federal Law and Guidance

In 2000, the HHS Office of Inspector General (OIG) found that oversight of recruitment – both by the federal government and by local IRBs – was “minimal and largely unresponsive to emerging concerns.”¹²¹ Despite these findings, the regulation of recruitment and enrollment in clinical trials has still not changed significantly.¹²² The concerns to which the OIG referred included pressure to recruit participants quickly, which could potentially undermine the informed consent process and lead to the enrollment of ineligible subjects. These concerns are even more compelling today.

Federal conflict of interest regulations govern most research conducted at academic medical centers as well as research in all settings involving drugs and devices that will be submitted to FDA for marketing approval. The PHS’s conflicts of interest regulations govern institutions that apply for research funding from PHS agencies, including the NIH, as well as the investigators participating in the research.¹²³ The FDA regulations cover clinical studies submitted in marketing applications for new drugs and biological products and marketing applications and reclassification petitions for medical devices.¹²⁴ However, these regulations do not provide for oversight of all relationships between industry and research institutions and investigators.¹²⁵ Moreover, even where FDA and PHS regulations do apply, they provide little guidance for investigators and industry regarding appropriate financial arrangements for clinical research. States’ oversight of research on human subjects has been insufficient, and few, if any, states have distinct requirements for managing relationships between industry and investigators.¹²⁶

1. PHS Regulations

PHS has issued conflicts of interest regulations that govern academic medical centers and other institutions that seek NIH and other federal government grants.¹²⁷ Under these regulations, grant-seeking institutions must require their investigators to disclose to the institutions “significant financial interests” “that would reasonably appear to be affected by the research for which PHS funding is sought” as well as significant financial interests “[i]n entities whose financial interests would reasonably appear to be affected by the research.”¹²⁸ These disclosures by investigators must be made annually, and updated when the institution applies for a grant and whenever the investigator incurs a new significant financial interest.¹²⁹

Significant financial interests include salary, royalties, or other payments (such as consulting or speaking fees) to the investigator or the investigator’s spouse or dependent children in excess of \$10,000 and equity interests owned by the investigator or the investigator’s spouse or dependent children in excess of \$10,000, or 5% of any single entity.¹³⁰ Institutions are required to take steps to manage, reduce, or eliminate any conflict of interest posed by a significant financial interest and report to NIH or other agency that they have done so.¹³¹ The regulations do not require that institutions report the nature of a conflict of interest or other details in the first instance, but they must be prepared to provide the funding agency with such additional information upon request.¹³²

The PHS regulations list a number of mechanisms to manage conflicts, including monitoring by independent reviewers, modification of the research plan, disqualification from

participation in all or portion of the research, divestiture of significant financial interests, severance of relationships that create actual or potential conflicts, and public disclosure of significant financial interests.¹³³ Notably, these requirements for identifying and managing conflicts apply only to investigator conflicts of interest. No regulations currently govern institutional conflicts of interest.

On May 8, 2009, HHS issued a notice of proposed rulemaking seeking comment on possible amendments to these conflict of interest regulations.¹³⁴ The nature and scope of the questions posed signal the potential for significant changes in current oversight of conflicts of interest. HHS sought comments related to both the obligations assigned to institutions as well as the role of government agencies in overseeing conflicts of interest.¹³⁵ In addition, HHS asked for feedback on various proposals to incorporate institutional conflicts of interest into the regulatory scheme, to enhance the identification and management of investigator conflicts by institutions, and to assure institutional compliance.

2. HHS Guidance Statement

In 2004, the Department of Health and Human Services issued a guidance statement on “Financial Relationships and Interests in Research Involving Human Subjects: Guidance for Human Subject Protection” (the “Guidance Statement”).¹³⁶ The Guidance Statement is non-binding, and sets forth questions for IRBs, institutions, and investigators engaged in research to consider when determining: (i) whether specific financial relationships create financial interests that may adversely affect the rights and welfare of subjects, and (ii) how potential or actual financial conflicts of interest should be managed or eliminated.

More specifically, the Guidance Statement recommends that the IRBs, institutions, and investigators consider which procedures would be helpful in identifying and managing financial conflicts of interest for institutions and investigators, such as: i) collecting and evaluating information regarding financial relationships related to research; ii) determining whether those relationships potentially cause a conflict of interest; and iii) determining the actions necessary to protect human subjects and ensure that those actions are taken. The Guidance Statement suggests that the IRB, institution, or investigator identify the entity to examine individual and/or institutional financial relationships and interests, although it does not go as far as to recommend which entity should conduct the examination. It also calls for consideration of who should be educated regarding financial conflict of interest issues and policies.

Regarding institutional oversight specifically, the Guidance Statement suggests that institutions consider, among other things: i) “[e]stablishing the independence of institutional responsibility for research activities from the management of the institution’s financial interests”; ii) “[e]stablishing conflict of interest committees (COICs) or identifying other bodies or persons and procedures” to manage or eliminate financial conflicts of interest; iii) “[e]stablishing clear channels of communication between COICs and IRBs”; iv) “[i]ncluding individuals from outside the institution in the review and oversight of financial interests in research”; and v) “[e]stablishing policies regarding the types of financial relationships that may be held by parties involved in the research and circumstances under which those financial relationships and interests may or may not be held.”¹³⁷ The Guidance Statement also has specific recommendations for investigators in clinical research, instructing that they consider, among other things, “the kind, amount, and level of detail of information to be provided to research subjects regarding the source of funding, funding arrangements, financial interests of parties involved in the research, and any financial interest management techniques applied.”¹³⁸

3. *FDA Regulations*

Clinical trials of drugs and medical devices are regulated by the FDA, which has adopted a conflict of interest policy to require that steps are “taken in the design, conduct, reporting, and analysis of [clinical trials] to minimize bias.”¹³⁹ The FDA obligates sponsors that submit marketing applications for drugs and devices to provide a list of the investigators who worked on “covered clinical stud[ies],” their financial interests as defined by the FDA, and the financial interests of their spouses and dependent children.¹⁴⁰ Covered studies are those that the study sponsor or the “FDA relies on to establish that the product is effective... or any study in which a single investigator makes a significant contribution to the demonstration of safety.”¹⁴¹ FDA conflict of interest oversight would not in general extend to “phase 1 tolerance studies or pharmacokinetic studies, most clinical pharmacology studies (unless they are critical to an efficacy determination), large open safety studies conducted at multiple sites, treatment protocols, and parallel track protocols,” or to post-approval trials that are not submitted in support of a supplemental marketing application.¹⁴²

As a general rule, the purpose of FDA’s oversight of financial interests is data integrity, not the protection of research participants.¹⁴³ The FDA requires submission of conflict of interest information only for the subset of studies about which it has the most data integrity concerns, primarily those used to establish a product’s efficacy, and only after the studies are complete.

For investigators conducting covered clinical studies, the FDA regulations require sponsors to disclose to the FDA the following financial interests: (1) compensation that could be influenced by the outcome of the clinical trial; (2) “significant payments of other sorts,” such as consulting or speaking fees, in excess of \$25,000 from the sponsor to the investigator; (3) any proprietary interest, such as a patent or trademark, in the tested product; and (4) any “significant equity interest” in the sponsor, defined to include equity in publicly-traded corporations in excess of \$50,000 and equity in other entities that are not readily valued by reference to public prices.¹⁴⁴ Notably, payments to cover “the costs of conducting the clinical study or other clinical studies” are expressly excluded from the definition of “significant payments of other sorts.”¹⁴⁵ In addition to disclosing information about financial ties, the FDA requires research sponsors to report on steps taken to minimize the potential for bias.¹⁴⁶ If an investigator’s disclosure raises data integrity questions, the FDA may audit the investigator’s data, require further analyses or studies, or refuse to use the entire clinical trial.¹⁴⁷

4. *Anti-Kickback Law*

The federal Anti-Kickback law¹⁴⁸ also has implications for the financial relationships of clinical investigators and manufacturers. The Anti-Kickback law prohibits remuneration in exchange for patient referrals to health services covered by Medicare, Medicaid, and other federally-funded programs. Specifically, the law bars any payment by an entity or individual to a physician for the purpose of inducing the physician to prescribe or use health care services reimbursed by a federal health program, including drugs and devices.¹⁴⁹ The federal government and several courts have held that even if only one purpose of a payment is to induce referrals, the transaction violates the law.¹⁵⁰ The Anti-Kickback law is a felony criminal statute which provides for criminal fines of up to \$25,000 and prison terms of up to 5 years for each violation. A separate statute provides for civil monetary penalties of up to \$50,000 per violation.¹⁵¹ Violators of the Anti-Kickback law also risk exclusion from participation in federal health programs such as Medicare and Medicaid.¹⁵² In addition, they could be sued by the govern-

ment or by a relator (an individual acting on the government's behalf) under the civil False Claims Act (FCA), on the theory that "a claim induced by a kickback is a fraudulent claim."¹⁵³ The FCA provides for treble damages.¹⁵⁴ As demonstrated by prominent prosecutions and settlements, financial arrangements between physicians and industry can violate the Anti-Kickback law, including payments to physicians who serve as consultants, members of scientific advisory boards, or company speakers who are also prescribers of the company's products.¹⁵⁵

Congress and the OIG have designated "safe harbors" for payment and business practices that, while potentially prohibited by the Anti-Kickback law, will not be prosecuted if every element of the safe harbor is met.¹⁵⁶ Failure to fulfill each safe harbor element does not mean that an activity is illegal – it means that an entity does not receive the benefit of the promise of non-prosecution. If an activity falls outside the safe harbor, the regulator or enforcement agency will employ its discretion to determine whether a statutory violation exists.¹⁵⁷

Recognizing that none of the safe harbors apply to clinical research, government regulators have advised sponsors to hew as closely as possible to the law's "personal services" safe harbor to avoid prosecution.¹⁵⁸ The personal services safe harbor requires that a contract for professional services for a clinical trial must: (i) be in writing and signed by both parties; (ii) specify all of the services the physician is to provide, each of which must be "reasonably necessary to accomplish the [agreement's] commercially reasonable business purpose"; (iii) specify the precise amount of time the physician will spend and the precise amount to be paid for his or her time; (iv) last for at least a year; (v) provide for compensation that is "consistent with fair market value in arms-length transactions"; and (vi) not "take[] into account the volume or value of any referrals or business otherwise generated between the parties for which payment may be made in whole or in part under Medicare or a State health care program."¹⁵⁹ The requirement that the agreement specify the payment amount raises particular issues for clinical research, which frequently relies upon per capita or per enrollee payments. With a per capita payment arrangement, it is difficult to set the global compensation in advance; while a trial likely has certain goals for the number of patients recruited, those goals may not be reached or may be exceeded. Post-approval clinical trials, where the sponsor does not provide the study medication for free, could also fail to meet the safe harbor requirement that the amount the physician is paid be unrelated to the volume or value of business generated between the parties.¹⁶⁰ While per capita payments are common practice, they must be structured carefully to meet the other prongs of the safe harbor.¹⁶¹

The OIG has also made clear that research contracts influenced by sales and marketing personnel are "particularly suspect."¹⁶² The OIG has focused on post-FDA approval "studies," suggesting that some are shams undertaken to induce physicians to use or prescribe the company's drugs or devices, thereby violating the Anti-Kickback law.¹⁶³ The OIG's 2003 Compliance Program Guidance for Pharmaceutical Manufacturers instructs that to "reduce risk, manufacturers should insulate research grant making from sales and marketing influences."¹⁶⁴ It is critical that a study design have valid scientific goals and merit, rather than seek to achieve promotional purposes.¹⁶⁵

5. Federal Guidance on Setting Fair Market Value

One linchpin of compliance with the Anti-Kickback law is compensation at fair market value (FMV).¹⁶⁶ Although the OIG has issued Advisory Opinions¹⁶⁷ addressing the application of the Anti-Kickback law to physician compensation in contexts other than research, such as compensation paid by a hospital to a physician to be on-call, none contains detailed direction on calculating the fair market value of a physician-investigator's research services, which

comprise both administrative and clinical tasks. Companies have been cautioned not to rely on values that may encompass a bias to overcompensation.¹⁶⁸ As applied to clinical research, this suggests that data on payment to physician-investigators for conducting clinical trials must be scrutinized to assure that the payments do not reflect physicians' ability to generate business, either because they themselves are high prescribers or because they can affect the prescription practices of others.

The Stark Law prohibiting physicians from referring patients to ancillary services in which the referring physician or a family member has a financial relationship¹⁶⁹ and the federal law precluding tax-exempt organizations from providing an excess benefit to individuals in a position to influence the organization's decisions¹⁷⁰ also rely upon the concept of fair market value or reasonable compensation as a touchstone for compliance. While these laws provide additional models of FMV, like the Anti-Kickback law, they do not establish a specific framework or guidance on setting FMV for clinical research.

The Stark Law defines the fair market value of, among other things, a physician's personal services as "the value in arms length transactions, consistent with the general market value."¹⁷¹ The regulations promulgated by the Centers for Medicare & Medicaid Services (CMS) on exceptions to the general rule against physician self-referral elaborate on the definition, providing,

"general market value" means... the compensation that would be included in a service agreement as the result of bona fide bargaining between well-informed parties to the agreement who are not otherwise in a position to generate business for the other party... Usually, the fair market price is... the compensation that has been included in bona fide service agreements with comparable terms at the time of the agreement, where the price or compensation has not been determined in any manner that takes into account the volume or value of anticipated or actual referrals.¹⁷²

Repealing earlier regulations that had sought to provide "bright line" rules for physician compensation,¹⁷³ CMS advised in the Federal Register that fair market value determinations are ultimately subject to a facts and circumstances test, and that "[r]eference to multiple, objective, independently published salary surveys remains a prudent practice for evaluating fair market value;" it emphasized that any "commercially reasonable methodology" could be used, and that the appropriate methodology depends, inter alia, upon the nature of the transaction and location.¹⁷⁴ CMS also noted that the fair market value of a physician's services as an administrator could differ from the fair market value of his or her clinical services.¹⁷⁵ Notably, in the clinical trials context, physician-investigators often engage in both types of services.¹⁷⁶

Internal Revenue Service (IRS) regulations on "reasonable compensation" for an individual who has "substantial influence" over a tax-exempt entity also incorporate the concept of fair market value and are therefore another potential source of guidance by analogy. The IRS regulations establish a rebuttable presumption that the compensation paid by a tax-exempt organization is reasonable (and therefore does not jeopardize the organization's tax exempt status or subject the individuals involved in the transaction to potential sanctions) if it is: (1) approved by a committee of individuals who do not themselves have a conflict of interest; (2) based on data regarding compensation of comparable individuals employed by comparable organizations; and (3) adequately documented.¹⁷⁷ The IRS has also issued guidance on valuing businesses, which some commentators have argued can be applied to setting physician compensation.¹⁷⁸

Neither AdvaMed nor PhRMA provides instruction on how to determine payment levels for investigators beyond an admonition to comply with the Anti-Kickback Act.¹⁷⁹ From the industry perspective, Pfizer's "Policy on Compensation to Investigators in Clinical Trials" provides that "financial compensation must be reasonable relative to compensation for similar clinical studies sponsored by the pharmaceutical/biotechnology industry in the country where the research is conducted."¹⁸⁰

6. Physician Payments Sunshine Act

Building on the national outcry for greater transparency in the relationship of industry and physicians, the Physician Payments Sunshine Act, pending federal legislation, would require disclosure of industry payments to physicians on a public website. State legislatures have already taken the lead in this area of policy reform, with at least five states and the District of Columbia mandating disclosure of industry payments and Massachusetts, Minnesota, and Vermont also requiring that such payments be made public.¹⁸¹ There are also at least two states which require that information about a clinical trial's funding be provided to prospective participants.¹⁸²

The Physician Payments Sunshine Act, which has received broad support from consumer, provider, and industry groups, would "provide for transparency in the relationship between physicians and manufacturers of drugs, devices, biologicals, or medical supplies for which payment is made under Medicare, Medicaid, or SCHIP."¹⁸³ In addition to bills introduced in the Senate in January 2009 and the House in July 2009, there are several other versions of the Act, as it has been incorporated into the various health reform bills and proposals.¹⁸⁴ Under all versions, manufacturers would be required to report payments or other transfers of value made to a physician.¹⁸⁵ They would also be required to report the physician's name, address, and specialty, the form and nature of the payment, and, if the payment is related to a particular drug, the name of the drug. The information would be posted on a website searchable by physician and location, in a manner that is clear and understandable, and easy to aggregate and download.¹⁸⁶ This website would serve as a valuable resource to policy-makers, prosecutors, and others with an interest in industry-physician financial relationships, although it would not substitute for investigators' disclosure of their financial ties directly to their institutions or to prospective research participants. Under certain versions of the Act, funding for clinical research and payments made pursuant to product development agreements would not be disclosed until after the clinical trial has been completed.¹⁸⁷

B. Government Oversight

1. The Failure of Administrative Agency Oversight

Government regulation of financial incentives for clinical trial recruitment and enrollment is poorly enforced.¹⁸⁸ Recent government investigations reveal that neither the NIH nor FDA is adequately enforcing extant conflict of interest regulations. A January 2009 OIG report concluded, among other findings, that: (i) the FDA does not routinely review financial information as part of its onsite inspections; (ii) the FDA cannot determine whether it has financial information for all clinical investigators because it does not have a complete list of investigators; (iii) when financial interests are disclosed, the FDA responds inconsistently, if at all; and (iv) 42% of marketing applications approved by the FDA were missing required financial information.¹⁸⁹

Likewise, a January 2008 OIG report leveled similar criticisms at the NIH, finding that: (i) NIH could not provide an accurate count of the conflict of interest reports it received from 2004 to 2006; (ii) NIH did not know what type of conflicts existed because for the most part grantee institutions' disclosures included no details; and (iii) NIH follow up on reported conflicts was inconsistent and infrequent.¹⁹⁰

2. Enforcement Actions and Settlement Agreements

Over the course of the past six months, federal and state prosecutors have focused their attention on the arena of clinical research, bringing major enforcement actions that seek to change particular company practices and, in the case of the prosecution in New Jersey against the Synthes Corporation, to effect reform of payment practices. While these cases have yielded important results and signal a mounting government focus on misconduct in research, they cannot provide the kind of systemic change or prospective guidance needed to frame federal policy on recruitment and enrollment or conflicts of interest. Moreover, enforcement actions identify specific investigator and institutional behaviors that the government deems illegal, but do not articulate best practices generally.¹⁹¹

The enforcement action that most clearly sought to achieve broader reform was the case brought by the New Jersey Attorney General against Synthes. Many physicians who had conducted clinical research on the Synthes device ProDisc, an artificial spinal disk approved by the FDA in 2006, stood to benefit financially if the device gained FDA approval.¹⁹² In May 2009, the New Jersey Attorney General entered into a settlement agreement with Synthes, ProDisc's manufacturer.¹⁹³ The Attorney General alleged that Synthes had violated the New Jersey Consumer Fraud Act by compensating physician-investigators with company stock and failing to disclose physician-investigators' financial interests to the FDA, as required by federal regulations. Under the settlement agreement, Synthes must submit all financial interest information, as defined in the FDA's conflict of interest regulations, to the IRB as part of each clinical investigator's initial IRB submission packet and/or request for approval. Through its contracts with clinical investigators, Synthes must obligate investigators to disclose their financial interests to research participants, if so required by the IRB reviewing the clinical trial.¹⁹⁴ When the FDA approves a Synthes device for marketing, the company must also disclose any physician-investigator financial interests to the general public via its website. Finally, the settlement agreement bars the company from reimbursing investigators with stock.¹⁹⁵ Concluding that the practice of compensating investigators with stock creates an "unacceptable conflict of interest," the Attorney General called upon federal regulators to address the practice at the national level. Recently, the New Jersey Attorney General has also launched investigations into the financial interests of investigators who performed studies for the device makers DePuy Orthopaedics and Medtronic.¹⁹⁶

In a 2008 settlement, Biovail Pharmaceuticals pled guilty to federal kickback and conspiracy charges for using sham studies to obtain physician loyalty to their product.¹⁹⁷ Specifically, Biovail used a "study," called the PLACE Program, as a mechanism to pay physicians to prescribe or recommend the drug Cardizem, L.A. to control high blood pressure. The Program essentially required participating physicians to prescribe Cardizem, L.A. to a cohort of patients about whom the prescriber would then complete two short multiple choice surveys over three patient visits. The physicians' payment was based upon the number of patients enrolled in the cohort and completion of the questionnaires – the more patients for whom the physician prescribed Cardizem, L.A., the more money the physician received from the manufacturer. The U.S. Attorney for Massachusetts determined that the payments of up to one thousand dollars

exceeded the fair market value of the medical prescribers' time necessary for the required tasks, assuming the study was even valid. Furthermore, the U.S. Attorney alleged that the program was not designed or implemented in a way to provide new or meaningful scientific data about Cardizem, L.A., but solely to increase the number of prescriptions generated.

3. *Lawsuits and Settlements*

Research participants who believe they have been harmed by investigator conflicts of interest have limited legal recourse. Courts have held that injured research participants cannot assert a claim for violation of the federal regulations designed to protect them,¹⁹⁸ but, in some cases, have allowed state law claims to proceed for lack of informed consent where the investigator stood to benefit financially from the positive outcome of a clinical investigation in which he or she is involved – e.g., where the investigator had money riding on the outcome – and the plaintiff was not informed of the conflict prior to consenting to participate.

For example, in *Wright v. Fred Hutchinson Cancer Center*, the estates and surviving relatives of deceased cancer patients who had participated in a clinical trial sued the Fred Hutchinson Cancer Research Center (the Hutch) and researchers, asserting that the defendants' failure to disclose the risks of trial participation and the financial interests of the Hutch and researchers involved in the study violated the rights of trial participants.¹⁹⁹ The clinical trial tested use of a monoclonal antibody to reduce the risk of graft-versus-host disease in bone marrow transplant recipients.²⁰⁰ In fact, the antibody caused graft rejections, cancer relapses, and new cancers, which the plaintiffs alleged caused premature death in trial participants. According to a *Seattle Times* exposé, the Hutch had licensed the commercial rights to the antibody being studied to a start-up company called Genetic Systems but retained a royalty interest.²⁰¹ The Hutch and the three researchers involved in the trial also held stock in Genetic Systems. In addition, one of the researchers had a seat on the Genetic Systems' scientific advisory board, another was employed as the company's medical director in addition to working for the Hutch, and the third was a consultant to the company.

The District Court for the Western District of Washington rejected the plaintiffs' federal claims for violation of rights arising from the regulations governing human subject research as well as the Nuremberg Code and the Declaration of Helsinki,²⁰² but allowed the state law fraud and informed consent claims to proceed to trial.²⁰³ The court ultimately rejected the fraud claim based on failure to prove the existence of the financial conflicts asserted.²⁰⁴ On the issue of informed consent, the jury found for the defendants, concluding that the participants had given their consent, and that a reasonably prudent fully informed person in their position would have made the choice to participate in the clinical trial.²⁰⁵

In another significant case, the court agreed to hear claims based in gross negligence and deceit where a hospital and physician-investigator failed to disclose a financial interest in the outcome of clinical research. In May 1999, Roger Darke died in a VEGF-2 gene therapy program conducted by Dr. Jeffrey Isner, chief of cardiovascular research at St. Elizabeth's Medical Center, within twenty-four hours of undergoing surgery in which the therapy was delivered. His widow brought suit against the hospital and doctors, alleging that had Darke known that a previous patient had died, and of the financial interests of the hospital and the physician-investigator, he would not have participated in the experimental program.²⁰⁶ Neither Isner nor the hospital disclosed to Darke or his wife, as part of the informed consent process, that, "if the gene therapy program was successful," they both "stood to profit financially in proportion to their ownership stake" in a company called Vascular Genetics.²⁰⁷ At the time the suit was filed, Isner and his heirs owned 20% of Vascular Genetics, which Isner helped found in 1997 to

support the experimental gene therapy treatment for coronary artery disease that he developed (the defendant hospital also owned 20%). The complaint alleged that Darke “was intentionally and maliciously treated as a human guinea pig in order to generate great financial profits for all defendants.”²⁰⁸ In June 2004, a Massachusetts Superior Court held that the doctor and hospital could be held liable for failing to disclose, as part of the informed consent process, their financial interests in the treatment that they recommended.²⁰⁹

In May 2005, the same court denied the Isner Estate’s²¹⁰ motion for summary judgment on Darke’s gross negligence claim, holding that enough evidence had been presented to support the allegation that Isner’s financial stake in the success of the gene therapy treatment may have compromised how the clinical trial was conducted.²¹¹ It also held that there was sufficient evidence to go forward with a deceit claim, for failure to disclose the financial relationships to Darke and his wife.²¹²

Although it did not see the inside of a courthouse, one of the most well-known informed consent cases involved the death of an 18-year old volunteer with ornithine transcarbamylase deficiency, Jesse Gelsinger, who died during his participation in a gene transfer study at the University of Pennsylvania. The lawsuit brought by his father against the university and investigators alleged that the investigators committed fraud by not revealing that a co-investigator, the University, and other university officials had financial relationships with Genovo, a biotechnology company, and stood to gain financially from the successful use of RDAd vectors.²¹³ The Complaint also alleged that the investigators had failed to inform Jesse of the risks of the study, that they had failed to inform Jesse or the FDA of adverse events experienced by other participants in the same trial as well as the death of monkeys in an earlier animal study, and that the investigators had allowed Jesse to participate in the study despite not meeting the inclusion criteria due to the fact that his liver was not functioning within the study’s 24-hour limit.²¹⁴ Jesse Gelsinger’s father learned that a “principal investigator, James Wilson, owned stock in... [the] company [he had] founded, which contributed \$4 million per year to human gene therapy research at the University . . . where the experiment took place,” and claimed that had Gelsinger known about these financial interests, “he would not have [participated] in the research study.”²¹⁵ The suit ended in a confidential settlement in 2000, six weeks after it was filed. In 2005, the University of Pennsylvania and Children’s National Medical Center agreed to pay over \$1 million in a False Claims Act settlement with the federal government, brought by the United States Attorney for the Eastern District of Pennsylvania, to resolve allegations that the institutions failed to disclose necessary information and misled the government about the benefits of the treatment (the three physician-investigators – including Wilson – were also parties to the settlement).²¹⁶ The federal investigation following Jesse Gelsinger’s death showed that Wilson withheld more information from the Gelsingers than just his financial interests, including prior negative test results.²¹⁷

THE ROAD TO REFORM

A. Preliminary Observations

Research is critical to the advancement of medical treatment and health. It must be structured to produce high quality data that facilitates the assessment of safety and efficacy in the population for whom the treatment will be used. The good of the enterprise requires that the clinical trial system sufficiently balance the costs and benefits to physicians and prospective trial participants to ensure the continued sufficient supply of researchers and subjects. The system must also be imbued with actual and perceived integrity – so that it produces scientifically reliable results, participants are safe, and people trust the system sufficiently to be willing to participate.

Clinical trial enrollment and recruitment practices are critical to protecting the rights and interests of enrollees as well as the scientific integrity of research. Potential enrollees are at risk if the process entails poor compliance with inclusion and exclusion criteria, inadequate informed consent, or pressure to enter or remain in a clinical trial. As reflected in government prosecutions and prominent cases that have come to light, these risks are exacerbated by financial incentives provided to investigators or institutions that may undermine their role as trustworthy gatekeepers of clinical research. In the current economic climate, potential enrollees are also more vulnerable as increasing numbers of individuals seek to participate in research either as a primary means of access to treatment or as a form of income.

Several premises that drove our analysis merit discussion as a preamble to our recommendations. Conflicts of interest in research are inevitable and do not in themselves signal unethical behavior – the goal is to eliminate those conflicts that pose excessive risk of distortion in judgment to the detriment of the study or research participant, which would be unethical, and reduce or manage those conflicts that pose a lesser degree of risk to avoid such distortions of judgment.²¹⁸

A general principle upon which our recommendations rest is that economic neutrality should prevail in compensation for research and reimbursement for treatment. Such a principle should eliminate the conflicts of interest that arise when the potential profit on research is so great that it may distort physicians' judgments to the potential detriment of their patients. This scenario arises most frequently in one of two ways – when the physician/investigator has some kind of investment whose value will increase with a successful trial outcome and when the physician/investigator's compensation for oversight of a patient in a trial well exceeds what the physician would be reimbursed if the patient continues treatment.

Physicians, lawyers, and ethicists alike generally agree that the opportunity to profit through an equity interest in the product that is subject to trial should be avoided entirely or in all but the most extraordinary of circumstances, in which case research subjects should be informed of these interests. Furthermore, fair market valuations of physician time should be comparable on an hourly or global basis to compensation for clinical work, to avoid the potential that research is more lucrative than treatment, and the attendant risk that such differences in compensation could factor into physician judgment.²¹⁹ This is particularly important because of the frequency with which physicians are referring their own patients to clinical trials, which also increases the likelihood of the therapeutic misconception on the part of patients/participants.

An overall bias of this section is that conflicts of interest in research are best addressed through the regulatory process, rather than through prosecutorial enforcement of laws such as the Anti-Kickback law.

B. Taking Stock: Current Oversight

As evidenced throughout this White Paper, the world of clinical research has changed in dramatic ways, but government oversight has not kept pace. Oversight and guidance of both investigator conflicts of interest and the recruitment, enrollment, and retention practices such conflicts could potentially influence is inadequate. Reporting by institutions to government of investigator conflicts occurs only after the research has been initiated or conducted, with inadequate information about the nature of the conflict or specific steps taken to eliminate or minimize the conflict in order to protect participants and research integrity. Current federal regulations fail to address institutional financial interests that could give rise to a conflict.

Institutional oversight, which exists primarily in academic medical centers, is also inadequate; within academic medicine, policies are not comprehensive; and faculty as well as institutional compliance with policies has been highly variable.²²⁰ Community hospitals by and large do not have conflicts committees to identify and manage conflicts, and IRBs lack the guidance, expertise, and in some cases, the information to execute this role effectively.²²¹ Further, for research conducted by individual physicians, physician groups, or private research institutes, no consensus exists among physicians about what comprises a conflict of interest and whether conflicts of interest present ethical dilemmas; most physicians deny that their own behavior is affected by conflicts of interest.²²² Finally, there is simply no extant mechanism either to gather information about compensation for clinical trials and other financial relationships between the sponsors and investigators, or to address any conflicts of interest that could influence recruitment and enrollment prior to commencement, much less completion, of the trial.

C. Government Reform

Government should undertake certain basic reforms to raise physician awareness about conflicts of interest, to bar forms of compensation for research that generate the greatest risk to participants, to provide guidance for managing other forms of compensation and financial interests held by investigators and institutions, and to increase transparency among all of the stakeholders involved with any particular trial. Government must also enhance its oversight of the recruitment, enrollment and retention practices attendant to clinical research, seeking more information about the conflicts at an earlier stage of the research process.

1. Compensation for Research

Per Capita Payments and Global Payments. Payments per enrollee (“per capita payments”) or global payment for the research project are common forms of reimbursement for clinical trials for research conducted within academic medicine and in community settings. While per capita payments create a direct incentive to recruit individual enrollees, the incentive is not problematic as long as the payment is not excessive. Likewise, global payments are an important vehicle to fund research as long as the amount of payment is appropriate and the calculation to determine compensation is well-delineated.

Current federal policy for per capita and global payments, although requiring FMV valuation, does not provide sufficient guidance about the methodology or principles by which fair market value for research compensation should be determined.²²³ Federal and state policy

statements, developed in the context of anti-kickback laws, are the primary regulations that guide FMV for research compensation. HHS should provide prospective, clear guidance for FMV in the context of clinical research.

Under the broad umbrella of the concept of FMV, businesses and personal services can be valued in different ways, including: (i) the classic economic formulation of whatever a willing buyer and willing seller agree upon in an arms-length negotiation; (ii) the average price set by the market of similarly situated buyers and sellers; or (iii) a calculation of projected costs.²²⁴ In the research setting, costs could include the cost of services provided by physicians, nurses and others, tests, procedures, and drugs, devices, and materials, staff training, the informed consent process, data collection, and adverse event reporting.

In the arena of financial relationships between industry and physicians, the first methodology has often yielded excessive payments for honoraria, travel, consulting fees, speakers bureau and advisory board participation, and other activities; these excessive payments have been widely recognized as a means to influence physicians' decisions about prescribing, recommendations by opinion leaders in the context of medical education, and physicians' conclusions in published study results. As highlighted by prominent prosecutions, payment for research – particularly for post-market “seeding” studies – may also be designed primarily to influence prescribing patterns.²²⁵ Overall, the payments for services to physicians, particularly in Phase IV trials that are most vulnerable to abuse as seeding studies, may have been inflated to yield a “market” result that encompasses the potential to influence referrals and change practice patterns. For this reason, neither the free market model of exchange between willing sellers and buyers nor the prices set by the aggregate of such transactions for particular types of studies should be used as the benchmark to set compensation for clinical research.

We recommend that the benchmark for compensation for physician services for research should be comparable payment for time and services for treatment. This will compensate physicians fairly for their time and services, and will assure that there are no hidden bonuses or incentives for physicians to recruit patients into research or to refer them to research rather than treatment. The determination of compensation should take into account factors such as geographic region, years in practice, board certification, and specialty.²²⁶ Significantly too, in order to avoid a disincentive for physicians to conduct research, the calculation of compensation for a clinical trial should include delineated reimbursement for all other expenses, including tests or interviews to screen patients, time seeking informed consent, tracking of enrollee participation, and data collection and reporting. Within academic medicine, the infrastructure is in place to undertake these responsibilities; for physicians in the community the costs may be different due to the need to hire staff to undertake these responsibilities or the need for physicians to perform certain tasks themselves. It is appropriate for per capita payments to include a factor for start up costs such as study design, patient recruitment, and staff training incurred, before participants are enrolled.

To accomplish this end, HHS should issue regulations that require payment neutrality as between treatment and research. The regulations should set forth a guiding principle that physicians and institutions should be fairly compensated for all legitimate aspects of research while avoiding payments that are excessive and may exert an undue influence on participant recruitment or other aspects of the clinical trials. In addition, federal guidelines should identify any expenses that are not permissible, provide guidance about factors such as geography and specialty that may be considered in setting FMV compensation, and require that the FMV calculation for per capita and global payments be set forth in writing.

Setting Limits – Other Payment Methodologies for Research. Per capita and global payments are acceptable approaches to compensate health care professionals and institutions for research. However, other methods of compensation create a direct conflict between the financial interests of investigators and the interests of potential participants and should be prohibited by federal regulation.

Finder's Fees. Professional organizations have rejected finder's fees as ethically unacceptable.²²⁷ These fees comprise payments to physicians, nurses, medical students and other participants in the research project solely for referring individuals to participate in a trial. While the frequency of such fees is debated, a recent survey of clinical research coordinators found that such fees are still used.²²⁸

HHS should bar any payment solely for a referral to a research trial as well as any payment methodology for screening potential participants or other services that conditions payment on the individual enrolling in the trial. Under this formulation, payment for screening participants on medical and psychosocial grounds could be reimbursed at FMV provided that the payment is made regardless of whether the person decides to enroll in the trial or is eligible to participate once screening tests and analysis are performed. Fees solely for the referral create an incentive to refer individuals regardless of whether they are appropriate for the study, a risk that is especially problematic when physicians with a long-term relationship with their patients refer them to research. Moreover, given that Medicare and Medicaid pay for the tests and elements of research that are standard treatment, finder's fees are likely to violate the federal and state Anti-Kickback laws, although this may not be well-understood by health care professionals.²²⁹

Bonuses for Recruitment and Retention. Like finder's fees, bonuses for recruiting a certain number of participants, meeting research recruitment goals in a particular timeframe, or retaining patients, create a direct conflict of interest by incentivizing physicians to recruit and retain individual patients to meet the bonus quotas or goals. The federal government should articulate the risks to potential enrollees and bar these forms of payment in research.

Payment with Equity. Payment of physicians who conduct research with equity in the research sponsor gives physicians a financial interest in the outcome of the clinical trial, creating significant risks both to enrollees and to the scientific integrity of the research. The federal government should prohibit this form of payment to physicians and other researchers, those in positions to affect the conduct of the research, or to entities conducting the research.²³⁰

2. Addressing Other Conflicts of Interest in Research

In addition to federal guidance for compensation for research, the current framework for federal policy to oversee investigators' conflicts of interest should be revised to specify conflicts that will disqualify a researcher from serving as an investigator. Further, regulations should enumerate requirements for identifying and managing other conflicts arising from the varied and frequent financial relationships between industry and physicians. Apart from payment for research, drug, device, and biotechnology companies that sponsor research may also provide other funding or remuneration to investigators, including honoraria for speaking engagements, consulting fees, payment for travel time and expenses, payment for service on an advisory board, and compensation for their intellectual contributions in the form of equity holdings or ownership rights in products (for example, royalty, patent, or license rights).

As proposed by the AAMC and most recently by the IOM Committee, holdings by investigators or their immediate family members²³¹ that provide a direct interest in the outcome of the research, such as stock or stock options in a privately held company or equity in a publicly traded company above a de minimis amount, should be barred absent a compelling rationale to permit the conflict.²³² The same policy should apply to intellectual property interests in a drug, device or other product investigated by the clinical trial. These holdings by investigators or their immediate family members give them a personal direct stake in the outcome of the research, which creates both the appearance of improper influence and the risk that the financial benefits, which can be substantial, could adversely affect both the interests of enrollees as well as the scientific integrity of the research. Only in circumstances where the research could not be conducted effectively or safely without the individual's participation, should an exception be allowed.²³³ Such cases presumably will be rare, arising, for example, when a physician has designed a device and is needed to consult on the surgical procedures for its implantation. In such instances, the physician should serve as a *consultant* rather than an investigator, and should not participate in key aspects of the research, including recruitment and enrollment, informed consent, and data collection and analysis. Instead, the physician should provide his or her technical expertise without playing other significant roles, as detailed in a written plan for managing the conflict. Moreover, where such intellectual property holdings are allowed, the FDA should be notified of the conflict, as well as the plan to reduce and manage it, prior to the commencement of research.

Service by a physician-investigator or immediate family members on the board of directors or as an officer of the company that sponsors the research or holds equity interests or ownership rights should also bar the physician-investigator from participating in the research, unless his or her technical expertise is essential to involvement as a consultant, as discussed above. Physician-investigators who play other leadership roles in privately-held, smaller corporations, including service on an advisory board or speakers bureau, or as a consultant, should also be barred from participating in the research, absent compelling circumstances in which participation should be limited to a consultant capacity, with prior notice to the FDA. Frequently, small closely-held companies are created to spin off the product research portion of an investigator's scientific work. These companies typically have a substantial stake in the outcome of the research through ownership rights in the product.

For publicly-held corporations, service on an advisory board or other financial relationships with the sponsor may also give rise to conflicts that must be addressed, although they fall short of requiring a ban on the relationship. Instead, conflicts committees should carefully scrutinize and evaluate the nature and longevity of the service and the amount of payments both historically and going forward in determining how to manage the conflict, and the federal government should adopt a mechanism for auditing such situations.

D. Enhancing Institutional Oversight of Conflicts of Interest

While government regulation can and should set policy parameters and direction and establish an effective audit process, institutional oversight of conflicts of interest will remain the primary vehicle to identify and manage conflicts of interest held by investigators and the institutions themselves. As reflected in recent congressional investigations and studies of institutional practice, a gap exists between recommended practices and policy adoption and adherence within academic medical centers.²³⁴ It is clear that academic medical centers have also fallen short in implementing reporting policies effectively through the creation of systems to collect information about investigator interests and to monitor compliance by investigators.

Institutional efforts to track investigators' financial relationships with industry will no doubt be enhanced by passage of national legislation requiring public reporting of physician/industry financial relationships. Public disclosure of payments by industry to physicians will be especially valuable in addressing conflicts of interest outside of academic medicine, where no system exists to report on conflicts of interest until after the research has been completed.

As reflected in studies of current practices and government investigations, financial relationships between industry and physician-investigators are prevalent, including payment for honoraria, consulting, travel, and continuing medical education.²³⁵ Institutions should evaluate each of these relationships to determine if the magnitude and form of the payment, the longevity of the relationship, or other factors suggest that the physician's relationship with the sponsor should be terminated or renegotiated or that the conflict of interest compels a different role for the physician in prospective research involving that sponsor.

1. Addressing Investigator Conflicts of Interest within Academic Medicine: Challenges and Solutions

Federal regulations as well as recommendations by the AAMC, the AAU and, most recently, the IOM provide a framework and guidance for institutional oversight of investigator conflicts of interests within academic medical centers. Under PHS guidelines, institutions are required to take steps to manage, reduce or eliminate any conflict of interest posed by a financial interest that meets the definition of "significant." However, the regulations do not obligate investigators to report all financial interests to the institution, do not require a written plan to manage all interests deemed to create a conflict, and do not require that the institution report the nature or extent of the conflict to PHS. Nor do the regulations state a process for review, substantive limits on the kinds of conflicts that may exist, or a required minimum response for conflicts that pose the greatest risks to participants and the integrity of the research.

Appropriately, HHS has sought recommendations to tighten and revise federal requirements for such oversight.²³⁶ In particular, the Request for Comments issued by HHS in May 2009 sought comments on a wide range of issues, including: (i) whether certain financial interests should be automatically reported to the institution rather than leave it up to each investigator to determine if the interests would "reasonably appear to be affected by the research"; (ii) whether all interests should be reviewed by an institutional committee; (iii) whether institutions should be required to create special conflicts of interest committees to review the information and make recommendations; and (iv) whether the regulations should bar certain conflicts or specify how they must be managed.

We recommend that investigators should be required to report all financial interests to an institutional committee for review regardless of the amount of the interests, rather than leaving it up to investigators to determine if the interest could reasonably be expected to affect the research. In fact, in order to be effective, institutions need to establish an internal database that investigators must update as information changes about their financial relationships with for-profit entities. While aggregating the information for all potential investigators is a massive undertaking for academic medical centers, it is the only effective means to address potential conflicts of interest proactively.

Federal policy should require that a committee review and manage conflicts of interest, and should specify requirements for the committee's expertise and obligations. The issue of whether a special conflicts of interest committee should be created to review and manage the conflicts is complex, and should be left up to the judgment of individual institutions. On the

one hand, a separate committee could bring additional expertise in financial arrangements. IRBs often lack this experience because they are often heavily comprised of clinicians. Conflicts committees may be farther removed from the clinicians whose research proposals are reviewed by the IRB. As a result, they may be more objective or more willing to act on conflicts that create either the appearance of a conflict or a risk of undue influence that may not be identified by clinicians immersed in research themselves. On the negative side of the equation, conflicts committees add a separate organizational structure and step to a process already criticized as too slow. If given additional resources, at least some IRBs could no doubt handle the additional responsibility in a process that is more streamlined. Giving IRBs the responsibility for managing conflicts, rather than creating a separate committee, may be especially valuable at community hospitals that do not conduct extensive research. In order to carry out the responsibility of overseeing conflicts of interest, IRBs could create a subcommittee that comprises individuals with financial expertise. If a separate conflicts committee is charged to address conflicts of interest, information about investigator conflicts for particular clinical trials should be reported to the IRB to inform its review of the proposed clinical trial as well as its obligation to review informed consent documents.

Finally, federal regulations bar any member of the IRB who has a “conflicting interest” from participating in review of a protocol.²³⁷ With guidance set by federal regulation, IRB policies should clearly delineate the interests that would be deemed “conflicting,” encompassing the broad array of financial relationships between industry and physicians.

2. Addressing Institutional Conflicts of Interest within Academic Medical Centers

As recognized in the recent IOM Committee report, institutional conflicts of interest have received far less scrutiny and attention from policymakers and others than the conflicts of investigators.²³⁸ Nonetheless, the recommendations of the AAMC and AAU provide important guidance, proposing that institutional conflicts, like investigator conflicts, should be identified, reviewed, and as needed, managed or eliminated. Significantly, the AAMC and AAU recommendations establish a rebuttable presumption that the institution should not conduct research if a conflict exists due to the financial interests of the institution or those in key leadership positions such as deans, department chairs, and division heads.²³⁹ Noting that institutional officers, such as the chief executive officer or the officers who oversee grants or technology transfer, may have an interest in strengthening the financial performance of the institution, the IOM Committee proposed that a committee or subcommittee of the board of directors should be charged to oversee the conflicts because of the board’s fiduciary duty to the institution and greater distance from day-to-day management.

We agree with the IOM recommendation that a committee of the board of directors should oversee institutional conflicts of interest in research. Members who serve on the committee should be independent of management. The board committee’s oversight should extend beyond the primary institutions, such as the medical school or university, to any not-for-profit institutes or for-profit corporate entities that are substantially controlled by or operate under the auspices of the medical school or university. These entities may receive substantial grants from industry or hold equity and property interests in the products studied in clinical trials by these entities or by the university or medical school. They also may have a small board of directors personally invested in or identified with the financial success of the entity.

The board committee charged to oversee institutional conflicts should produce general conflict of interest policies that are available to all, both within and outside the institution;

ideally, they should be posted on the institution's website. Like the committee that manages investigator conflicts, the board committee should report its findings and conclusions regarding any particular investigator or proposed trial to the IRB. As with management of investigator conflicts, effectively overseeing institutional conflicts will depend in the first instance on capturing the relevant interests across the many parts of the institution where they may arise: the office of technology transfer, the development office, the grants office, grants to individual departments or their chairs, and the holdings of executive management.

3. Overseeing Conflicts of Interest in the Community Setting

In community settings, FDA and PHS require sponsors and investigators to be responsible for the review and management of investigator conflicts of interest prior to the time that research begins. Independent IRBs do not necessarily see conflicts review as part of their responsibilities, and, as with the rest of the IRB process, no government agency reviews IRB decisions at the time they are made to ensure that the IRB is acting appropriately. Institutional conflicts of interest are unregulated. We recommend that the FDA and PHS regulations be revised to set forth guidelines for the process and substance of conflicts of interest review in community settings. Such regulations would need to include a provision requiring physicians to make relevant financial information available for review.

Outside of academic medicine, private research institutes, companies that sponsor research, or CROs or SMOs retained by the sponsor, oversee the conduct of research projects. By and large, conflicts committees do not exist to review potential conflicts held by the investigator or the entity, such as a physicians group, conducting the research. The sponsor, or a CRO or SMO acting as its agent, is ill-suited to review conflicts of interest that are generated through either the means or magnitude of payment for research or by other financial relationships with investigators.

IRBs, whether independent or based in a community hospital or other facility, should be charged with the review of conflicts of interest held by investigators and entities conducting research in community settings. IRBs could create a separate committee on conflicts of interest with appropriate expertise to establish policies for the IRB's conflicts review. Alternatively, conflicts committees acting as a subcommittee of the IRB or as a separate committee could review individual protocols. Reviewing conflicts of interest and formulating recommendations about managing the conflicts is a substantial additional responsibility that should be reflected in additional fees for protocol review to assure that IRBs have the resources to undertake this task.

Assigning this responsibility to independent IRBs is an imperfect solution; but it is also the only possible avenue that could serve this function. As commentators have pointed out, sponsors or CROs and SMOs acting on their behalf can manipulate the system of IRB review by choosing IRBs that have a reputation or practice for lax review.²⁴⁰ Independent IRBs are for-profit entities; some may place the financial success of the entity above the need to devote extensive resources to thorough review of each protocol. At the same time, other commentators have noted that independent IRBs often operate more efficiently than IRBs in academic medicine; the IRB membership is smaller, the meetings are more frequent, the members are compensated for their time, in contrast to their counterparts in academic medicine, and a stream of revenue supports the activity. In addition, IRBs in academic medicine and community hospitals face their own distinct pressures, including the fact that the IRB members are reviewing the research proposals of their peers and colleagues, and serve on the IRB in addition to their other responsibilities.

Federal regulations should provide clear guidance to IRBs about the nature and scope of information they should review, the standards for the review, and the alternatives for eliminating, minimizing, or managing a conflict. This guidance should apply to conflicts of interest facing both investigators and institutions, such as physician groups and private research institutes. By and large, federal regulations and policies should be similar for IRBs within and outside academic medicine. As with academic medicine, institutional conflicts of interest should be broadly defined to include both financial interests held by the institution as well as financial interests of leadership within the institution and their spouses and children. In addition, since physician practices and research centers or institutes are far smaller in terms of size and diversity of revenue, revenues from the sponsor for research or for any other purpose that exceed a specified threshold of the overall revenue of the entity should preclude the site from participation in research. Federal regulations should also spell out clearly the obligation of physicians or institutions acting on their behalf to report information about compensation for research and other financial interests to IRBs or conflicts committees.

4. Achieving Transparency

Consistent with the national movement towards transparency in industry-physician relationships, federal law should require disclosure of payments for conducting clinical trials and other relevant financial interests. Specifically, before research commences, sponsors should report to the FDA and academic institutions should report to the granting federal agency equity and ownership interests as well as all payments, above a de minimis amount, to the investigator and the investigator's institution or practice group by the company whose product is under review in the clinical trial. Federal policy should consider mandating disclosure to potential enrollees of the method of compensation for research as well as information about conflicts of interest held by investigators and institutions.²⁴¹

5. Enhanced Training for Investigators

Current federal guidelines provide no specific requirements for conflicts of interest training for individuals who serve as investigators within or outside academic medicine. Yet studies of physician knowledge and awareness of financial conflicts of interest demonstrate the need for specific training about the nature of conflicts, the potential harm, and the ways that conflicts can be managed or eliminated.²⁴² This training should be mandatory for all investigators who conduct clinical research within and outside of academic medical centers.

In addition, physicians in community settings who conduct research often have limited training in or understanding of research methodology, the ethical underpinnings of research, or the differences in their roles as treating physician and as research investigator.²⁴³ For this reason, for physician investigators outside of academic medicine who conduct research, training should cover key elements of research: the importance of inclusion and exclusion criteria and informed consent, the ethical and scientific issues posed by particular research methods such as double blind placebo-controlled studies, and their obligations as an investigator compared to their role as a treating physician. This training should be mandatory for all investigators, except those who conduct only a limited number of hours of research in a given year or are not involved in enrollment and recruitment or data analysis.

ENDNOTES

- ¹ See CENTER FOR HEALTH & PHARM. LAW & POLICY, SETON HALL UNIV. SCH. OF LAW, WHITE PAPER, DRUG AND DEVICE PROMOTION: CHARTING A COURSE FOR POLICY REFORM (2009) [hereinafter PROMOTION WHITE PAPER].
- ² See, e.g., INST. OF MED. OF THE NAT'L ACADS., CONFLICT OF INTEREST IN MEDICAL RESEARCH, EDUCATION, AND PRACTICE 6-8 (Bernard Lo & Marilyn J. Field eds., 2009) [hereinafter IOM REPORT]; AAMC-AAU ADVISORY COMM. ON FIN. CONFLICTS OF INTEREST IN HUMAN SUBJECTS RESEARCH, PROTECTING PATIENTS, PRESERVING INTEGRITY, ADVANCING HEALTH: ACCELERATING THE IMPLEMENTATION OF COI POLICIES IN HUMAN SUBJECTS RESEARCH 22 (2008) [hereinafter AAMC-AAU 2008 COI REPORT]; Troyen A. Brennan et al., *Health Industry Practices That Create Conflicts of Interest: A Policy Proposal for Academic Medical Centers*, 295 JAMA 429, 429-33 (2006).
- ³ Documents recently released in litigation suggest the broad scope of the practice in promoting certain drugs; the documents reveal a plan for an entity hired by a pharmaceutical company to prepare close to 60 articles to promote one of its drugs, published under the names of prominent physicians who did not direct the research findings or article preparation. See Natasha Singer, *Senator Moves to Block Medical Ghostwriting*, N.Y. TIMES, Aug. 19, 2009, at B1, <http://www.nytimes.com/2009/08/19/health/research/19ethics.html?ref=business>. See also Natasha Singer & Duff Wilson, *Medical Editors Push for Ghostwriting Crackdown*, N.Y. TIMES, Sept. 17, 2009, at B1, http://www.nytimes.com/2009/09/18/business/18ghost.html?_r=2&scp=1&sq=medical%20editors%20push%20for%20ghostwriting&st=cse.
- ⁴ See, e.g., PROMOTION WHITE PAPER, *supra* note 1, at 4; IOM REPORT, *supra* note 2, at 3-1-3-28.
- ⁵ See PROMOTION WHITE PAPER, *supra* note 1, at 7.
- ⁶ See, e.g., Kevin P. Hill et al., *The ADVANTAGE Seeding Trial: A Review of Internal Documents*, 149 ANNALS INTERNAL MED. 251, 251-58 (2008); Press Release, Department of Justice, *New Jersey Company Agrees to Plead Guilty to Kickbacks and Conspiracy Charges and Pay More Than \$22 Million Dollars in Criminal Fines* (May 16, 2008), <http://www.usdoj.gov/usao/ma/Press%20Office%20-%20Press%20Release%20Files/May2008/bioval/Press%20Release.pdf> (announcing guilty plea and settlement of case where company conducted study the purpose of which was to “accelerate the uptake” of one of the company’s drugs).
- ⁷ Gina Kolata, *Lack of Study Volunteers Hobble Cancer Fight*, N.Y. TIMES, Aug. 2, 2009, at A1, available at <http://www.nytimes.com/2009/08/03/health/research/03trials.html>. See also Kenneth A. Getz et al., *Assessing the Impact of Protocol Design Changes on Clinical Trial Performance*, 15 AM. J. THERAPEUTICS 450, 456 (2008); Ezekiel J. Emanuel et al., *The Costs of Conducting Clinical Research*, 21 J. CLINICAL ONCOLOGY 4145, 4147 (2003).
- ⁸ There is some evidence that the lack of reimbursement for certain aspects of clinical research (such as meeting with potential participants and working through the informed consent process), coupled with the burden of filling out forms and completing paperwork, deter many physicians from serving as investigators. Analyzing the competing incentives in the oncology market is particularly difficult. It was possible until recently for physicians to profit from the spread between the cost at which they purchased chemotherapy drugs and the cost at which they were reimbursed for them. This source of profit would not be available to them in the context of a research trial, because research medications are typically supplied by the research sponsor. Such complexities in the market make hewing the line between under- and over-payment complicated.
- ⁹ Susan Gilbert, *Trials and Tribulations*, 38 HASTINGS CTR. REP. 14, 15 (2008).
- ¹⁰ Getz, *supra* note 7, at 456.
- ¹¹ Emilie Reymond, *New Project to Boost Patient Participation in US Trials*, OUTSOURCING-PHARMA.COM, Sept. 19, 2007, <http://www.outsourcing-pharma.com/Clinical-Development/New-project-to-boost-patient-participation-in-US-trials>.
- ¹² *Id.*; Shari Roan, *Medical Clinical Research Slows for Lack of Patients*, L.A. TIMES, Mar. 14, 2009, available at <http://articles.latimes.com/2009/mar/14/science/sci-clinical-trials14>.

- ¹³ JILL A. FISHER, *MEDICAL RESEARCH FOR HIRE: THE POLITICAL ECONOMY OF PHARMACEUTICAL CLINICAL TRIALS* 3 (2009).
- ¹⁴ Jean Ortiz, *Paid Studies Draw More Interest in Sour Economy*, BOSTON GLOBE, Jan. 5, 2009, available at http://www.boston.com/news/world/europe/articles/2009/01/05/paid_studies_draw_more_interest_in_sour_economy/.
- ¹⁵ FISHER, *supra* note 13, at 130.
- ¹⁶ *Miami Test Center Lures Poor Immigrants as Human Guinea Pigs*, Nov. 2, 2005, http://www.bloomberg.com/apps/news?pid=specialreport_index2&sid=amgWGeDrNJtg&refer=news.
- ¹⁷ FISHER, *supra* note 13, at 130.
- ¹⁸ *In re Zyprexa Prods. Liability Litig.*, 253 F.R.D. 69, 106 (E.D.N.Y. 2008).
- ¹⁹ *Id.*
- ²⁰ *Id.*; Joseph Loscalzo, *The NIH Budget and the Future of Biomedical Research*, 354 NEW ENG. J. MED. 1665, 1665 (2006).
- ²¹ Robert Steinbrook, *The NIH Stimulus – The Recovery Act and Biomedical Research*, 360 NEW ENG. J. MED. 1479, 1479-81 (2009).
- ²² See Carl Coleman, *Foreword*, 32 SETON HALL L. REV. 489, 489-92 (2003).
- ²³ Robert Steinbrook, *Gag Clauses in Clinical-Trial Agreements*, 352 NEW ENG. J. MED. 2160, 2161 (2005).
- ²⁴ *Id.*
- ²⁵ Alan R. Fleischman & Jason E. Klein, *Clinical Research in the Private Office Setting – Ethical Issues*, 113 TRANSACTIONS AM. CLINICAL AND CLIMATOLOGICAL ASS’N 126, 129 (2002) (“For years physician-investigators in academic settings have accrued substantial secondary gain to themselves or their departments from clinical trials, but as compared to the private practice setting, in academia direct personal financial gain has rarely been possible.”).
- ²⁶ IOM REPORT, *supra* note 2, at 6-8.
- ²⁷ Gilbert, *supra* note 9, at 15 (noting that contract research organizations often pay community physicians to recruit their own patients).
- ²⁸ Tracy E. Miller & Carol R. Horowitz, *Disclosing Doctors’ Incentives: Will Consumers Understand and Value the Information?*, 19 HEALTH AFFAIRS 149, 151 (2000) (“Trust in physicians is generally high, although potentially vulnerable as patients learn more about their physicians’ financial incentives.”).
- ²⁹ Paul S. Appelbaum et al., *Therapeutic Misconception in Clinical Research: Frequency and Risk Factors*, 26 IRB: ETHICS & HUMAN RESEARCH 1, 1-8 (2004); Paul S. Appelbaum et al., *Correction and Clarification*, 26 IRB: ETHICS & HUMAN RESEARCH 18, 18 (2004).
- ³⁰ Norman G. Levinsky, *Nonfinancial Conflicts of Interest in Research*, 347 NEW ENG. J. MED. 759, 759 (2002); Fleischman & Klein, *supra* note 25, at 129.
- ³¹ See Andrew Pollack, *Death in Gene Therapy Treatment Is Still Unexplained*, N.Y. TIMES, Sept. 18, 2007, available at <http://www.nytimes.com/2007/09/18/health/18gene.html>.
- ³² Complaint, *Gelsinger v. Trustees of the Univ. of Pa.*, No. 000901885 (Pa. Ct. Com. Pl. Sept. 18, 2000), available at <http://www.sskrplaw.com/links/healthcare2.html>; Robin Fretwell Wilson, *Estate of Gelsinger v. Trustees of University of Pennsylvania*, in HEALTH LAW & BIOETHICS: CASES IN CONTEXT 251-52 (Sandra H. Johnson et al. eds., 2009) (the case also resulted in a False Claims Act suit by the U.S. Attorney charging that “the study had produced toxicities in humans that should have resulted in termination,” that reports to the FDA and

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NIH misrepresented clinical findings, and that the informed consent document excluded crucial information regarding possible dangers to study participants).

- ³³ *Id.* The Complaint also alleged that Genovo, a biotech company founded by one of the researchers, had a right to license any resulting products.
- ³⁴ Josh Goldstein, *After Hip Replacements, a Lawsuit*, PHILA. INQUIRER, June 30, 2008, available at http://www.dufffirm.com/docs/Hip%20Replacement%20Lawsuit_Philadelphia%20Inquirer_06-30-08.pdf.
- ³⁵ See Civil Docket Report, McKenzie et al. v. Garino, et al., No. 060501864 (Pa. Ct. Com. Pl. May 12, 2006), available at https://fjdefile.phila.gov/dockets/zk_fjd_public_qry_03.zp_dktrpt_frames?case_id=060501864.
- ³⁶ Kurt Eichenwald & Gina Kolata, *Drug Trials Hide Conflicts for Doctors*, N.Y. TIMES, May 16, 1999, at 1, available at <http://www.nytimes.com/1999/05/16/business/drug-trials-hide-conflicts-for-doctors.html>.
- ³⁷ Parham's heart condition should have excluded him from the study, but since he did not sue the physician, it was never definitively established that the study drug led to the deterioration of his condition and his need for a pacemaker.
- ³⁸ Hill, *supra* note 6, at 252.
- ³⁹ *Id.*
- ⁴⁰ *Id.* at 253.
- ⁴¹ *Id.*
- ⁴² Thomas M. Burton & David Armstrong, *Grassley Probes Kuklo Study*, WALL ST. J., May 19, 2009, at A6; Barry Meier & Duff Wilson, *Medical School Says Former Army Surgeon Hid Ties to Medtronic*, N.Y. TIMES, July 15, 2009, at B3, available at <http://www.nytimes.com/2009/07/15/business/15device.html> (reporting that the physician executed the consulting agreement three days after completing the university's conflict of interest forms indicating the absence of any conflicts).
- ⁴³ See, e.g., AAMC TASK FORCE ON FIN. CONFLICTS OF INTEREST IN CLINICAL RESEARCH, PROTECTING SUBJECTS, PRESERVING TRUST, PROMOTING PROGRESS: POLICY AND GUIDELINES FOR THE OVERSIGHT OF INDIVIDUAL FIN. INTERESTS IN HUMAN SUBJECTS RESEARCH 14 (2001) [hereinafter AAMC 2001 COI REPORT].
- ⁴⁴ Responsibility of Applicants for Promoting Objectivity in Research for Which PHS Funding Is Sought, 42 C.F.R. §§50.601-50.607 (2009). The National Science Foundation (NSF) has an almost identical policy for those applying for NSF funding. See National Science Foundation, Frequently Asked Questions Concerning the DHHS Objectivity in Research Regulations and the NSF Investigator Financial Disclosure Policy (July 24, 1996), <http://www.nsf.gov/pubs/stis1996/faqinfin/faqinfin.txt>.
- ⁴⁵ Elizabeth A. Boyd et al., *Implementation of Financial Disclosure Policies to Manage Conflicts of Interest: How Seven University of California Campuses Deal with Their Research Relationships*, 23 HEALTH AFFAIRS 206, 207 (2004).
- ⁴⁶ Mark Hall et al., *Community Hospital Oversight of Clinical Investigators' Financial Relationships*, 31 IRB: ETHICS & HUMAN RESEARCH 7, 9-10 (2009) (finding that three of nine health care organizations that owned or operated nonacademic community hospitals had no institutional processes for detecting or reviewing financial relationships between investigators and sponsors; the six that did review financial relationships did so through their institution's IRB with technical or administrative assistance from administrative staff or a subcommittee of the IRB).
- ⁴⁷ Janet M. Lis & Melinda G. Murray, *The Ins and Outs of Independent IRBs*, 2 J. HEALTH & LIFE SCIENCES LAW, 73, 75 (2008).
- ⁴⁸ Fleischman & Klein, *supra* note 25, at 127-28.

- ⁴⁹ IOM REPORT, *supra* note 2, at 2-2. Conflicts of interest are not limited to investigators; they can also arise at the level of the research institution. The IOM defines institutional conflicts of interest as situations when there is the potential for the secondary interests of the institution or its senior officials to have an undue influence.
- ⁵⁰ See Jesse A. Goldner, *Dealing with Conflicts of Interest in Biomedical Research: IRB Oversight as the Next Best Solution to the Abolitionist Approach*, 28 J. L. MED. & ETHICS 379, 380 (2000).
- ⁵¹ Harold E. Glass, *Do Clinical Grant Payment Practices in Phase 3 Clinical Trials Influence Subsequent Clinical Investigator Prescribing Behavior?* 7 DISEASE MGMT. 77, 80 (2004). See also Paula S. Katz, *In-Office Research Can Trip Up Even the Most Ethical Doctors*, ACP INTERNIST (2008), <http://www.acpinternist.org/archives/2008/01/research.htm> (“Most research is reimbursed per patient to account for physician and staff time as well as any needed special facilities or equipment, such as a secure locked area to store drugs and records.”); PARTNERS HUMAN RESEARCH COMM., POLICY ON PAYMENTS IN CLINICAL TRIAL AGREEMENTS (2005), http://healthcare.partners.org/phsirb/Guidance/Policies_Procedures/bonus_policy_april20_2005.pdf (“[T]ypically a sponsor pays the hospital or other entity on a per-subject basis in order to reimburse costs proportionally.”); Hal S. Katz, *Clinical Trials: Alternative Revenue Stream or Just Another Potential Lawsuit*, 16 HEALTH LAWYER 1, 10 (2004) (“Generally, physicians negotiate a fixed-price per patient with a payment schedule.”).
- ⁵² Glass, *supra* note 51, at 80. Where research participants have health insurance, some of the care they receive in the context of the trial may be covered. In that case, the sponsor would only cover non-routine protocol-induced care.
- ⁵³ Emanuel, *supra* note 7, at 4147.
- ⁵⁴ *Id.*
- ⁵⁵ Robert Zuercher, *Investigators as Suppliers*, APPLIED CLINICAL TRIALS ONLINE (Apr. 1, 2007), <http://appliedclinicaltrialsonline.findpharma.com/appliedclinicaltrials/article/articleDetail.jsp?id=416540>.
- ⁵⁶ See *infra* text accompanying notes 166-178.
- ⁵⁷ Fred Eaton & Yoram Levy, *Fair Market Value*, PHARM. EXECUTIVE (Sept. 1, 2005), available at <http://pharmexec.findpharma.com/pharmexec/article/articleDetail.jsp?id=177954>.
- ⁵⁸ Likewise, whenever reimbursement for treatment exceeds research compensation, the physician-investigator may be discouraged from considering research participation, which is also problematic.
- ⁵⁹ Karine Morin et al., *Managing Conflicts of Interest in the Conduct of Clinical Trials*, 287 JAMA 78, 81 (2002). A payment structure under which researchers prefer industry compensation to government compensation for research raises concerns. Multiple reviews of the medical literature show that articles reporting on clinical trials funded by industry are more likely to conclude that the trial results support the efficacy or safety of the studied drug or device, than are articles published about clinical trials without industry support. See IOM REPORT, *supra* note 2, at 4-6-4-7 (surveying literature supporting the conclusion that industry support is associated with pro-industry conclusions). There are many possible explanations for this. It may reflect bias on the part of investigators or their industry funders but it may merely indicate that for-profit companies invest in the products that are likely to succeed. There is no evidence that industry-supported trials are of lower quality than trials with alternate sources of support. See *id.* at 4-7.
- ⁶⁰ Steve Stoller, *Financing Clinical Trials Research at Kaiser Permanente*, 5 PERMANENTE J. 41, 41 (2001).
- ⁶¹ Getz, *supra* note 7, at 457; Kenneth A. Getz, *Have We Pushed Our Pis Too Far?*, APPLIED CLINICAL TRIALS ONLINE (Sept. 1, 2005), <http://appliedclinicaltrialsonline.findpharma.com/appliedclinicaltrials/article/articleDetail.jsp?id=176904>.
- ⁶² Lori Shields et al., *Sponsors: Pay Heed*, APPLIED CLINICAL TRIALS ONLINE (Aug. 1, 2007), <http://appliedclinicaltrialsonline.findpharma.com/appliedclinicaltrials/article/articleDetail.jsp?id=445944>. The website of the University of Michigan Medical School’s Grant Review & Analysis Office explains that “A contract that garners \$1800 for an IRB Fee and \$1562 for advertising (\$1250 + 25%) regardless of patient enrollment is much more viable if it enrolls no patients in competitive enrollment than one that has the costs built into the per patient amount.” See Univ. of MI Med. Sch. Grant Review & Analysis Office, Corporate

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- Budgeting Issues, http://www.med.umich.edu/medschool/grants/budgeting_issues.htm (last visited Sept. 8, 2009).
- ⁶³ Press Release, Office of the New Jersey Attorney General, *Landmark Settlement Reached with Medical Device Maker Synthes* (May 5, 2009), <http://www.nj.gov/oag/newsreleases09/pr20090505a.html>.
- ⁶⁴ *Id.*
- ⁶⁵ *Assurance of Voluntary Compliance* (May 1, 2009), at Section C, Part 1(d), <http://www.nj.gov/oag/newsreleases09/pr20090505a-Synthes-avc-signed.PDF>.
- ⁶⁶ PhRMA, PhRMA's Principles on Conduct of Clinical Trials and Communication of Clinical Trial Results (2009) [hereinafter PhRMA Clinical Trials Principles], Principle 3(c), http://www.phrma.org/files/042009_Clinical%20Trial%20Principles_FINAL.pdf.
- ⁶⁷ AdvaMed, Code of Ethics on Interactions with Healthcare Professionals (July 1, 2009) [hereinafter AdvaMed Code] at 10, 19, <http://www.advamed.org/NR/rdonlyres/61D30455-F7E9-4081-B219-12D6CE347585/0/AdvaMedCodeofEthicsRevisedandRestatedEffective20090701.pdf> (providing that research grants should “not be linked directly or indirectly to the purchase of Medical Technologies” and that “compensation should be based on fair market value for the services provided”). See discussion of Anti-Kickback law *infra* Section III.A.4.
- ⁶⁸ Eichenwald & Kolata, *supra* note 36, at 1 (“Drug companies and their contractors offer large payments to doctors, nurses and other medical staff to encourage them to recruit patients quickly. . . . Special cash bonuses for signing up specified numbers of people by a given date . . . are becoming part of the landscape.”). See also, e.g., *New Jersey Company Agrees to Plead Guilty to Kickbacks and Conspiracy Charges and Pay More Than \$22 Million Dollars in Criminal Fines*, *supra* note 6 (physician-investigators paid \$250 for enrolling between 1 and 5 patients, an additional \$500 for enrolling between 6 and 10 patients, and an additional \$750 for enrolling between 11 and 15 patients); Anna Wilde Mathews, *Infected Data: Fraud, Errors Taint Key Study of Widely Used Sanofi Drug*, WALL ST. J. (May 1, 2006) at A1 (physician-investigators paid \$100 for each patient enrolled, \$150 when they submitted results, and \$150 when all questions were resolved).
- ⁶⁹ Bonnie Brascia, *Better Budgeting for Patient Recruitment*, PHARM. EXECUTIVE (May 1, 2002), available at <http://pharmexec.findpharma.com/pharmexec/article/articleDetail.jsp?id=17940>.
- ⁷⁰ Carl Canavan et al., *Integrating Recruitment into eHealth Patient Records*, APPLIED CLINICAL TRIALS ONLINE (June 1, 2006), <http://appliedclinicaltrialsonline.findpharma.com/appliedclinicaltrials/article/articleDetail.jsp?id=334569> (citing CENTERWATCH, *A 2003 Assessment of Competitive Trial Enrollment Practices*, in PHARMACEUTICAL R&D STATISTICAL SOURCEBOOK 2004/2005 109 (2004)).
- ⁷¹ INST. OF MED. OF THE NAT'L ACADS., *ETHICAL CONDUCT OF CLINICAL RESEARCH INVOLVING CHILDREN* 21 (Marilyn J. Field & Richard E. Behrman eds., 2004).
- ⁷² PhRMA Clinical Trials Principles, *supra* note 66, Principle 3(c).
- ⁷³ Pfizer, Policy on Compensation to Investigators in Clinical Trials, http://www.pfizer.com/responsibility/research_clinical_trials/compensation_investigators.jsp (last visited Sept. 8, 2009).
- ⁷⁴ James A. Christensen & James P. Orlowski, *Bounty-Hunting and Finder's Fees*, 27 IRB: ETHICS & HUMAN RESEARCH 16, 16 (2005); Eichenwald and Kolata, *supra* note 36 (“[D]octors do not even have to conduct trials to get paid: There are finder’s fees for those who refer their patients to other doctors conducting research.”); Stuart E. Lind, *Finder's Fees for Research Subjects*, 323 NEW ENGL. J. MED. 1710, 1710 (1990) (“[D]iscussions with some persons attending a national meeting on the conduct of clinical research revealed that [finder’s] fees have been proposed or offered in a variety of locations around the country, although the exact frequency remains unknown.”).
- ⁷⁵ See Section III.A.4 and 5, *infra*. If the referring physician is paid regardless of whether the referred participant enters the clinical trial, the parties can avoid the appearance or fact of an illegal payment in exchange for a referral.

- ⁷⁶ AMERICAN COLL. OF PHYSICIANS, ETHICS MANUAL, 5th Edition, http://www.acponline.org/running_practice/ethics/manual/ethicman5th.htm (last visited Sept. 18, 2009) (“Giving or accepting finder’s fees for referring patients to a research study generates an unethical conflict of interest for physicians.”); AMERICAN MED. ASS’N, FINDER’S FEES: PAYMENT FOR THE REFERRAL OF PATIENTS TO CLINICAL RESEARCH STUDIES, CEJA Report 2-I-94 (1994), <http://www.ama-assn.org/ama1/pub/upload/mm/369/65b.pdf> (“[T]he acceptance of compensation for the referral of patients to a research study (a finder’s fee) is unethical.”).
- ⁷⁷ University of Florida Institutional Review Boards, Finder’s Fees’ for the Identification of Potential Research Subjects, <http://www.irb.ufl.edu/docs/op-finders.doc> (last visited Sept. 8, 2009); University of Pennsylvania, Office of Regulatory Affairs, Guidelines for Payment for Recruitment of Subjects in Human Research (Apr. 21, 2006), <http://www.upenn.edu/regulatoryaffairs/Pdf/guidelinespaymentforrecruitment.pdf>.
- ⁷⁸ Pfizer, *supra* note 73.
- ⁷⁹ See Section III.A.4 and 5, *infra*.
- ⁸⁰ Joelle Y. Friedman et al., *Perspectives of Clinical Research Coordinators on Disclosing Financial Conflicts of Interest to Potential Research Participants*, 4 CLINICAL TRIALS 272, 275 (2007).
- ⁸¹ In an earlier white paper, we recommended that physician-industry relationships be made transparent and the gifts, meals, and other perks that industry provides doctors be banned outright. PROMOTION WHITE PAPER, *supra* note 1, at 4-5.
- ⁸² Eric G. Campbell et al., *A National Survey of Physician-Industry Relationships*, 356 N. ENGL. J. MED. 1742, 1746 (2007).
- ⁸³ Eric Campbell et al., *Looking a Gift Horse in the Mouth: Corporate Gifts Supporting Life Sciences Research*, 279 JAMA 995, 997 (1998).
- ⁸⁴ Federal legislation passed in 1980 allows investigators and institutions to elect to retain title to the intellectual property arising out of their government-funded research in return for, among other things, a promise to commercialize their research findings. University and Small Business Patent Procedures Act (also known as the Bayh-Dole Act), 35 U.S.C. §§ 200-212 (2009).
- ⁸⁵ AAMC TASK FORCE ON FIN. CONFLICTS OF INTEREST IN CLINICAL RESEARCH, PROTECTING SUBJECTS, PRESERVING TRUST, PROMOTING PROGRESS II: PRINCIPLES AND RECOMMENDATIONS FOR OVERSIGHT OF AN INSTITUTION’S FIN. INTERESTS IN HUMAN SUBJECTS RESEARCH 2-3 (2002) [hereinafter AAMC 2002 COI REPORT].
- ⁸⁶ Eric Campbell et al., *Institutional Academic Industry Relationships*, 298 JAMA 1779, 1782-83 (2007).
- ⁸⁷ David Armstrong, *Delicate Operation: How a Famed Hospital Invests in Device It Uses and Promotes – Cleveland Clinic Set Up Fund that Has Stock in Maker of Heart Surgery System – Dr. Cosgrove’s Multiple Roles*, WALL ST. J., December 12, 2005, at A1.
- ⁸⁸ IOM REPORT, *supra* note 2, at S-14; PhRMA Clinical Trials Principles, *supra* note 66, Principle 3(c). The IOM defines “compelling circumstance” as one where the “individual’s participation is essential for the conduct of the research,” with the condition that the institution establish an effective mechanism to manage the conflict and protect the integrity of the research. It offers as an example the situation where a researcher with a conflict of interest has unique expertise or skill with implanting and adjusting a complex new medical device and this expertise is needed to carry out an early-stage clinical trial safely and competently. IOM REPORT, *supra* note 2, at 3-15. The AAMC defines “compelling circumstances” as “those facts that convince the institution’s [conflicts of interest] committee that a financially interested individual should be permitted to conduct human subjects research,” and recommends that conflicts committees evaluate, among other things, the nature and level of risk of the research, the magnitude of the interest, and the extent to which the research could affect the interest. AAMC 2001 COI REPORT, *supra* note 43, at 10-11. The AAMC also gives as an example an inventor of an implantable medical device who receives royalty income as well as compensation from the manufacturer for training physicians on the device’s implantation who might nevertheless be permitted to participate in research on the device. *Id.* at 8 n.12. In the case of Jesse Gelsinger, the notion of compelling or “unusual” circumstances was central. The University of Pennsylvania’s Conflict of Interest Standing Committee (CISC) purportedly determined that “unusual circumstances” would justify allowing Dr. James M. Wilson, an

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investigator and founder of Genovo, to participate in the research while continuing to have a substantial equity stake in the company. However, one member of the Committee resigned over the accuracy of CISC's minutes after maintaining that CISC had never agreed that there had actually been a finding of unusual circumstances sufficient to justify Wilson's status as a trial investigator. Wilson, *supra* note 32, at 251-52.

⁸⁹ See AAMC 2002 COI REPORT, *supra* note 85, at 6-7.

⁹⁰ AAMC 2001 COI REPORT, *supra* note 43, and AAMC 2002 COI REPORT, *supra* note 85.

⁹¹ AAMC 2001 COI REPORT, *supra* note 43, at 14-16.

⁹² *Id.* at 14.

⁹³ For a contrarian view, see C.K. Gunsalus, et al., *Mission Creep in the IRB World*, 312 SCIENCE 1441, 1441 (2006) ("...IRBs are pressured to review an expanding range of issues from research design and conflicts of interest to patient privacy. These are beyond the scope of research protection and are best left to others."); Joel S. Weissman et al., *Opinions of IRB Members and Chairs Regarding Investigators' Relationships with Industry*, 1 J. EMPIRICAL RESEARCH ON HUMAN RESEARCH ETHICS 3, 6 (2008) (reporting that 2% of IRB chairpersons and members surveyed believed that investigators' financial relationships with industry should not be considered by the IRB).

⁹⁴ See Weissman, *supra* note 93, at 7 (reporting that one third of IRB chairpersons and members surveyed believed that IRBs should consider only those financial relationships with industry deemed a conflict by the conflicts committee while two thirds believed that IRBs should review all financial relationships); Mark Barnes & Patrik S. Florencio, *Investigator, IRB and Institutional Financial Conflicts of Interest in Human-Subjects Research: Past, Present and Future*, 32 SETON HALL L. REV. 525, 558 (2003) (noting that the AAMC recommends that when the conflicts committee and the IRB disagree about how to manage a particular conflict, the disagreement should be resolved in favor of the more stringent approach, while the National Human Research Protections Advisory Committee recommended that the IRB be given the power of de novo review, even if that meant that the conflicts committee's recommendations were weakened or rejected).

⁹⁵ The AAMC "strongly recommends that the COI process be separate from the IRB, although with clear channels of communication between them." AAMC 2001 COI REPORT, *supra* note 43, at 8.

⁹⁶ Weissman, *supra* note 93, at 7.

⁹⁷ *Id.* at 7-8.

⁹⁸ Christine Vogeli et al., *Policies and Management of Conflicts of Interest within Medical Research Institutional Review Boards*, 84 ACAD. MED. 488, 492 (2009) (finding that one in five IRB chairs did not feel confident that appropriate disclosure of IRB members' industry relationships was made in every case and that one in four IRBs lacked written policies for managing IRB member conflicts that were disclosed); Eric Campbell et al., *Financial Relationships between Institutional Review Board Members and Industry*, 355 NEW ENGL. J. MED. 2321, 2325-26 (2006) (finding that relationships between industry and IRB members occur frequently, that more than half of those surveyed reported that their IRB lacked a formal process for disclosure of industry relationships, that more than 40% did not know whether their IRB had a formal definition of conflict of interest, and that 6.9% had freely participated in the discussion of a protocol or voted on it despite a conflict of interest).

⁹⁹ AAMC-AAU 2008 COI REPORT, *supra* note 2, at 2.

¹⁰⁰ SUSAN EHRLINGHAUS & DAVID KORN, AAMC, U.S. MEDICAL SCHOOL POLICIES ON INDIVIDUAL FINANCIAL CONFLICTS OF INTEREST: RESULTS OF AN AAMC SURVEY 3-4 (2002).

¹⁰¹ *Id.* at 6. The authors comment that "a higher response on this measure would assure that conflicts issues are fully examined and resolved and inform IRB review, prior to IRB approvals."

¹⁰² Susan Ehringhaus et al., *Response of Medical Schools to Institutional Conflicts of Interest*, 229 JAMA 665, 668-69 (2008).

- ¹⁰³ See, e.g., Burton & Armstrong, *supra* note 42; Meier & Wilson, *supra* note 42; Gardiner Harris, *Top Psychiatrist Didn't Report Drug Makers' Pay*, N.Y. TIMES, October 4, 2008 at A1, available at <http://www.nytimes.com/2008/10/04/health/policy/04drug.html>.
- ¹⁰⁴ See Hall, *supra* note 46, at 9.
- ¹⁰⁵ 21 C.F.R. §§ 54.4(a)(3) and 54.5(a) (2009). The FDA regulations require sponsors to disclose to the FDA the following financial interests: (1) compensation that could be influenced by the outcome of the clinical trial; (2) “significant payments of other sorts,” such as consulting or speaking fees, in excess of \$25,000 from the sponsor to the investigator; (3) any proprietary interest, such as a patent or trademark, in the tested product; and (4) any “significant equity interest” in the sponsor, defined to include equity in publicly-traded corporations in excess of \$50,000 and equity in other entities that are not readily valued by reference to public prices. Notably, payments to cover “the costs of conducting the clinical study or other clinical studies” are expressly excluded from the definition of “significant payments of other sorts.”
- ¹⁰⁶ 21 CFR § 312.52 (2009).
- ¹⁰⁷ Lis & Murray, *supra* note 47, at 75.
- ¹⁰⁸ See *id.*
- ¹⁰⁹ IRBs can earn accreditation by the Association for the Accreditation of Human Research Protection Program (AAHRPP), which provides standards, procedures and a regular inspection. AAHRPP, Accredited Organizations, <http://www.aahrpp.org/www.aspx?PageID=11> \$1\$100 (last visited Sept. 9, 2009).
- ¹¹⁰ See Hall, *supra* note 46, at 11.
- ¹¹¹ *Id.* at 8, 10-11. A majority of respondents said that per capita payments “constituted the bulk or vast majority of financial relationships in the studies they oversaw for their health care organizations.” The study noted that equity interests and intellectual property interests with the industry sponsor were involved in only small number of the studies the respondents oversaw. Respondents generally reported that per capita payments are reviewed much more frequently than consultancy arrangements.
- ¹¹² 42 C.F.R. § 50.604(a) (2009) (“Each institution must ... inform each Investigator of [its conflict of interest policy], the Investigator’s reporting responsibilities, and of these regulations.”) The NIH also requires that researchers complete training in human subjects research ethics. See NIH, *Required Education in the Protection of Human Research Participants*, available at <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-039.html> (last visited Sept. 21, 2009); NIH, *Frequently Asked Questions for the Requirement for Education on the Protection of Human Subjects*, available at http://grants.nih.gov/grants/policy/hs_educ_faq.htm (last visited Sept. 21, 2009); Debra A. DeBruin et al., *Educational Approaches to the Responsible Conduct of Clinical Research: An Exploratory Study*, 82 ACAD. MED. 1, 32 (2007), available at http://www.ahc.umn.edu/img/assets/23396/BIOETHICS_Educational_Approaches.pdf.
- ¹¹³ 21 C.F.R. § 54.4(b) (2009). Sponsors are charged with selecting investigators who are “qualified by training and experience as appropriate experts to investigate the drug,” 21 C.F.R. § 312.53(a) (2009), and with providing them with information about the drug, 21 C.F.R. §§ 312.23(a)(5) and 312.55 (2009). Investigators are assigned responsibility for “protecting the rights, safety, and welfare of subjects under [their] care[.]” 21 C.F.R. § 312.60 (2009).
- ¹¹⁴ Ehringhaus & Korn, *supra* note 100, at 6.
- ¹¹⁵ Jason Dana & George Loewenstein, *A Social Science Perspective on Gifts to Physicians from Industry*, 290 JAMA 252, 254 (2003).
- ¹¹⁶ *AMA Again Rejects CEJA Report*, MEETINGSNET (June 30, 2009), http://meetingsnet.com/medicalmeetings/cme_rules_regs/0630-ama-rejects-ceja-report/.
- ¹¹⁷ Association of Clinical Researchers and Educators, <http://www.acreonline.org/> (last visited Sept. 9, 2009).
- ¹¹⁸ *Id.*

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- ¹¹⁹ IOM REPORT, *supra* note 2, at 6-8.
- ¹²⁰ Jill A. Fisher, *Practicing Research Ethics: Private-Sector Physicians & Pharmaceutical Clinical Trials*, 66 SOC. SCI. & MED. 2495, 2500-01 (2008).
- ¹²¹ OFFICE OF INSPECTOR GEN., U.S. DEP'T OF HEALTH AND HUMAN SERVS., RECRUITING HUMAN SUBJECTS: PRESSURES IN INDUSTRY-SPONSORED CLINICAL RESEARCH 3 (2000), *available at* <http://www.oig.hhs.gov/oei/reports/oei-01-97-00195.pdf>.
- ¹²² For an excellent overview of the legal framework for oversight of human subjects research, including recruitment and enrollment, *see* CARL COLEMAN, JERRY MENIKOFF, JESSE A. GOLDNER, AND NANCY DUBLER, *THE ETHICS AND REGULATION OF RESEARCH WITH HUMAN SUBJECTS* (2005).
- ¹²³ *See supra* note 112.
- ¹²⁴ 21 C.F.R. §§ 54.1-54.5 (2009).
- ¹²⁵ For example, neither the PHS nor the FDA conflict of interest regulations cover industry-funded clinical trials that are never submitted in support of a marketing application to the FDA.
- ¹²⁶ Despite the proliferation of state anti-kickback laws, few have directly addressed financial arrangements for clinical research. California law precludes pharmaceutical companies from paying fees to physicians for referring their patients to a clinical research program, but allows evaluation fees for legitimately performed evaluations of the results of the program. CAL. BUS. & PROF. CODE § 650 (West's Ann. 2008).
- ¹²⁷ Responsibility of Applicants for Promoting Objectivity in Research for Which PHS Funding Is Sought, 42 C.F.R. §§ 50.601-50.607 (2009).
- ¹²⁸ 42 C.F.R. § 50.604(c)(1) (2009).
- ¹²⁹ 42 C.F.R. § 50.604(c)(2) (2009).
- ¹³⁰ 42 C.F.R. § 50.603 (2009). *Significant Financial Interest* means: 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). *Id.*
- ¹³¹ 42 C.F.R. §§ 50.604 and 50.605 (2009).
- ¹³² 42 C.F.R. §§ 50.604(g) (2) and (3) (2009).
- ¹³³ 42 C.F.R. § 50.605(a) (2009).
- ¹³⁴ Responsibility of Applicants for Promoting Objectivity in Research for Which Public Health Service Funding Is Sought and Responsible Prospective Contractors; Request for Comments, 74 Fed. Reg. 21610, 21610-21613 (May 8, 2009).
- ¹³⁵ Among the questions posed by HHS are whether the current de minimis thresholds (\$10,000 and 5% ownership interest in any single entity) should be changed and whether certain types of significant financial interests should be deemed conflicts of interest as a matter of federal regulation, rather than investigator or institutional judgment. *Id.*
- ¹³⁶ 69 Fed. Reg. 26394, 26394-26397 (May 12, 2004).
- ¹³⁷ *Id.* at 26396.
- ¹³⁸ *Id.* at 26397.
- ¹³⁹ 21 C.F.R. §§ 54.1-54.6; 21 C.F.R. 54.1(b) (2009).
- ¹⁴⁰ 21 C.F.R. § 54.4 (2009).

- ¹⁴¹ 21 C.F.R. § 54.2(e) (2009).
- ¹⁴² *Id.*
- ¹⁴³ FDA evaluates the information disclosed by the sponsors “to determine the impact of any disclosed financial interests on the reliability of the study.” 21 C.F.R. § 54.5(a) (2009).
- ¹⁴⁴ 21 C.F.R. § 54.4(a)(3) (2009).
- ¹⁴⁵ 21 C.F.R. § 54.2(f) (2009).
- ¹⁴⁶ 21 C.F.R. § 54.5(a) (2009).
- ¹⁴⁷ 21 C.F.R. § 54.5(c) (2009).
- ¹⁴⁸ 42 U.S.C. § 1320a-7b (2009).
- ¹⁴⁹ For example, in September 2007, the New Jersey U.S. Attorney reached a settlement with five companies that comprised 95% of the hip and knee replacement industry. The companies were charged with violating the Anti-Kickback law by compensating hundreds of surgeons to use the companies’ products exclusively. Press Release, Department of Justice, *Five Companies in Hip and Knee Replacement Industry Avoid Prosecution by Agreeing to Compliance Rules and Monitoring* (Sept. 27, 2007), <http://www.usdoj.gov/usao/nj/press/files/pdf/files/hips0927.rel.pdf>.
- ¹⁵⁰ *See, e.g.*, *United States v. Greber*, 760 F.2d 68, 71-72 (3rd Cir. 1985) (holding that the Anti-Kickback law is violated if only one purpose of a payment is to induce referrals, even if the transaction reflected reasonable compensation for the services rendered).
- ¹⁵¹ 42 U.S.C. § 1320a-7a(a)(7) (2009).
- ¹⁵² 42 U.S.C. § 1320a-7 (2009). *See* Kathleen M. Boozang & Simone Handler-Hutchinson, “*Monitoring Corporate Corruption: DOJ’s Use of Deferred Prosecution Agreements in Health Care*,” 35 AM. J. LAW & MED. 89, 89-90 (2009) (discussing the “irremediable harm” that can result from exclusion).
- ¹⁵³ James G. Sheehan & Jesse A. Goldner, *Beyond the Anti-kickback Statute: New Entities, New Theories in Healthcare Fraud Prosecutions*, 40 J. HEALTH L. 167, 178 (2007).
- ¹⁵⁴ 31 U.S.C. §§ 3729–3733 (2009). Paying a kickback can give rise to False Claims Act liability if it induces a health care provider to submit a false claim for reimbursement to the government. *See, e.g.*, *U.S.A. ex rel. Kennedy and Matos v. Aventis Pharms.*, Case No. 03 C 2750, 2008 U.S. Dist. LEXIS 100444 (E.D. Ill. Dec. 10, 2008) (dismissing False Claims Act claim based on violation of Anti-Kickback law where plaintiff failed to allege a link between payments made by the defendant and a claim for reimbursement); *U.S. ex rel. Schmidt v. Zimmer, Inc.*, 386 F.3d 235 (3rd Cir. 2004) (allowing plaintiff’s FCA claim that an orthopedic equipment manufacturer paid kickbacks to hospitals in the form of incentives and bonuses in order to induce purchases of its equipment to proceed).
- ¹⁵⁵ *See generally* House Committee on Oversight and Government Reform Hearing, Testimony of Lewis Morris, Chief Counsel to the Inspector Gen., U.S. Dep’t of Health and Human Servs. (Feb. 9, 2007), <http://oversight.house.gov/documents/20070209123330-60758.pdf>.
- ¹⁵⁶ 42 U.S.C. §§ 1320a-7b(c) & (d) (2009); Office of Inspector General, U.S. Dep’t of Health & Human Services, *Safe Harbor Regulations*, <http://oig.hhs.gov/fraud/safeharborregulations.asp> (last visited Sept. 9, 2009) and *Safe Harbor Regulations Archive*, http://oig.hhs.gov/fraud/safeharborregulations_archive.asp (last visited Sept. 9, 2009).
- ¹⁵⁷ OFFICE OF INSPECTOR GEN., U.S. DEP’T OF HEALTH AND HUMAN SERVS., *FEDERAL ANTI-KICKBACK LAW AND REGULATORY SAFE HARBORS* (1999), <http://oig.hhs.gov/fraud/docs/safeharborregulations/safefs.htm>.
- ¹⁵⁸ 42 C.F.R. § 1001.952(d) (2009). *See* Office of Inspector Gen., U.S. Dep’t of Health and Human Servs., *OIG Compliance Guidance for Pharmaceutical Manufacturers*, 68 Fed. Reg. 23731, 23736 (May 5, 2003)

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[hereinafter “Compliance Guidance”] (providing that clinical trial agreements “should be structured to fit in the personal services safe harbor whenever possible.”).

- ¹⁵⁹ 42 C.F.R. § 1001.952(d)(5) (2009).
- ¹⁶⁰ Thomas N. Bulleit, Jr. & Joan H. Krause, *Kickbacks, Courtesies or Cost-Effectiveness?: Application of the Medicare Antikickback Law to the Marketing and Promotional Practices of Drug and Medical Device Manufacturers*, 54 FOOD DRUG L.J. 279, 306 n.124 (1999).
- ¹⁶¹ *See id.* at 316.
- ¹⁶² Compliance Guidance, *supra* note 158, at 23736.
- ¹⁶³ *See* OFFICE OF INSPECTOR GEN., U.S. DEP’T OF HEALTH & HUMAN SERVS., PROMOTION OF PRESCRIPTION DRUGS THROUGH PAYMENTS AND GIFTS 4-6 (1991), available at <http://oig.hhs.gov/oei/reports/oei-01-90-00480.pdf>; OFFICE OF INSPECTOR GEN., U.S. DEP’T OF HEALTH & HUMAN SERVS., PRESCRIPTION DRUG PROMOTION INVOLVING PAYMENTS AND GIFTS: PHYSICIANS’ PERSPECTIVES 8, 9 (1992), available at <http://oig.hhs.gov/oei/reports/oei-01-90-00481.pdf>.
- ¹⁶⁴ Compliance Guidance, *supra* note 158, at 23736.
- ¹⁶⁵ The Compliance Guidance explains that post-marketing research activities should be “especially scrutinized to ensure that they are legitimate and not simply a pretext to generate prescriptions of a drug.” *Id.* at 23735. *See also* Bulleit & Krause, *supra* note 160, at 308-309.
- ¹⁶⁶ *See, e.g.*, Compliance Guidance, *supra* note 158, at 23735 (“Payments for research services should be fair market value for legitimate, reasonable, and necessary services.”).
- ¹⁶⁷ Advisory Opinions are issued by the OIG “to one or more requesting parties about the application of the OIG’s fraud and abuse authorities to the party’s existing or proposed business arrangement”; they are “legally binding on the Department of Health and Human Services . . . and the requesting party or parties.” Office of the Inspector Gen., U.S. Dep’t of Health & Human Servs., Advisory Opinions Frequently Asked Questions, <http://oig.hhs.gov/fraud/advisoryopinions/aofaq.asp> (last visited Sept. 10, 2009).
- ¹⁶⁸ Ann Brandt & Daryl Johnson, *Fair Market Value: With No Formal Fair Market Value Guidelines Imposed by the Government, How ‘Fair’ Is It for Pharma to Play by the Rules?*, 29 PHARM. EXECUTIVE (2009).
- ¹⁶⁹ 42 U.S.C. § 1395nn (2009).
- ¹⁷⁰ 26 U.S.C. § 501(c)(3) (2009); 26 U.S.C. § 4958 (2009).
- ¹⁷¹ 42 U.S.C. § 1395nn(h)(3) (2009).
- ¹⁷² 42 C.F.R. § 411.351 (2009).
- ¹⁷³ The regulations had provided that payment for physician’s services would be deemed to be fair market value if the rate paid was either (1) “less than or equal to the average hourly rate for emergency room physician services in the relevant physician market, provided there are at least three hospitals providing emergency room services in the market” or (2) “determined by averaging the 50th percentile national [annual] compensation level for physicians with the same physician specialty in at least four [of six agency-specified] surveys and dividing by 2,000 hours.” 42 CFR § 411.351 (2006). In repealing the regulations in 2007, CMS stated that it was difficult to obtain hourly rates paid by competitor hospitals and that the specified surveys were out-of-date or unavailable. *See* Medicare Program; Physicians’ Referrals to Health Care Entities With Which They Have Financial Relationships (Phase III), 72 Fed. Reg. 51012, 51015 (2007).
- ¹⁷⁴ Medicare Program; Physicians’ Referrals to Health Care Entities With Which They Have Financial Relationships (Phase III), 72 Fed. Reg. 51012, 51015 (2007). *See also* Medicare Program; Physicians’ Referrals to Health Care Entities With Which They Have Financial Relationships (Phase II), 69 Fed. Reg. 16054, 16107 (Mar. 26, 2004) (“We appreciate the commenter’s desire for clear ‘bright line’ guidance. However, the statute covers such a wide range of potential transactions that it is not possible to verify and list appropriate benchmarks

or objective measures for each. Moreover, the definition of ‘fair market value’ in the statute and regulation is qualified in ways that do not necessarily comport with the usage of the term in standard valuation techniques and methodologies. For example, the methodology must exclude valuations where the parties to the transactions are at arm’s length but in a position to refer to one another.”).

- ¹⁷⁵ *Id.* at 51016.
- ¹⁷⁶ *Id.* See, e.g., Emanuel, *supra* note 7, at 4147 (finding that 32% of a physician-investigator’s time was spent on non-clinical activities).
- ¹⁷⁷ 26 C.F.R. § 53.4958-6 (2009).
- ¹⁷⁸ Internal Revenue Service, Business Valuation Guidelines, http://www.irs.gov/irm/part4/irm_04-048-004.html#d0e10 (last visited Sept. 10, 2009). See, e.g., Andrea M. Ferrari et al., *Determining ‘Fair Market Value’ for Physician Services: The New ‘Big Question’ for Life Sciences Companies*, 3 LIFE SCIENCES 9, 10 (2009) (setting forth the cost, income, and market approaches to determining the FMV of an asset).
- ¹⁷⁹ AdvaMed Code, *supra* note 67, at 2; PhRMA Clinical Trials Principles, *supra* note 66, at 15-16.
- ¹⁸⁰ Pfizer, *supra* note 73.
- ¹⁸¹ D.C. CODE § 48-833.01 (2009); ME. REV. STAT. ANN. TIT. 22, § 2698-A (2009); Mass. Ann. Laws ch. 111N, § 6 (2009); MINN. STAT. § 151.47(f) (2009); VT. STAT. ANN. TIT. 18, § 4632 (2009); 2009 W. VA. ACTS 108 (transferring authority to require the reporting of pharmaceutical advertising costs from the Pharmaceutical Cost Management Council to the Governor’s Office of Health Enhancement and Lifestyle Planning).
- ¹⁸² See, e.g., CAL. HEALTH & SAFETY CODE § 24173(c) (2009) (requiring that research participants be informed of any sponsor, funding source, or manufacturer of a drug or device, and the organization “under whose general aegis the experiment is being conducted.”); N.J. STAT. § 26:14-4 (2009) (requiring disclosure where medical research involves “persons with cognitive impairments, lack of capacity, or serious physical or behavioral conditions and life-threatening diseases.”).
- ¹⁸³ Physician Payments Sunshine Act, S. 301, 111th Cong. (2009).
- ¹⁸⁴ See, e.g., America’s Affordable Health Choices Act of 2009, H.R. 3200, 111th Cong. (2009).
- ¹⁸⁵ See, e.g., S. 301 §2 (amending the Social Security Act to include §1128G (a) and (g)(10)(B)(i)).
- ¹⁸⁶ *Id.*
- ¹⁸⁷ See, e.g., H.R. 3200 § 1451 (amending the Social Security Act to include §§ 1128H(a)(4) and (5)) and providing for delayed reporting of payments made pursuant to product development agreements and clinical investigations).
- ¹⁸⁸ Generally, PHS and FDA have broad authority to enact regulations with regard to conflicts of interest. Under the Public Health Service Act and other applicable law, HHS has authority to regulate institutions engaged in HHS conducted or supported research involving human subjects. For HHS conducted or supported research, the funding agency may impose additional conditions as necessary for the protection of human subjects. 45 CFR § 46.124. Under the Federal Food, Drug, and Cosmetic Act, FDA has the authority to regulate Institutional Review Boards (IRBs) and investigators involved in the review or conduct of FDA-regulated research.
- ¹⁸⁹ OFFICE OF INSPECTOR GEN., U.S. DEP’T OF HEALTH AND HUMAN SERVS., THE FOOD AND DRUG ADMINISTRATION’S OVERSIGHT OF CLINICAL INVESTIGATORS’ FINANCIAL INFORMATION (2009), available at <http://www.oig.hhs.gov/oei/reports/oei-05-07-00730.pdf>. The report found that FDA had not documented review of the information in 31% of the applications.
- ¹⁹⁰ OFFICE OF INSPECTOR GEN., U.S. DEP’T OF HEALTH AND HUMAN SERVS., NATIONAL INSTITUTES OF HEALTH: CONFLICTS OF INTEREST IN EXTRAMURAL RESEARCH (2008), available at <http://www.oig.hhs.gov/oei/reports/oei-03-06-00460.pdf>.

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- ¹⁹¹ Companies become aware of investigations of particular practices within the industry early in their inception; by the time a settlement is actually announced, the industry has frequently addressed the offensive behavior. Consequently, settlements sometimes address out-of-date behaviors.
- ¹⁹² Reed Abelson, *Financial Ties Are Cited as Issue in Spine Study*, N.Y. TIMES, Jan. 30, 2008, at A1, available at <http://www.nytimes.com/2008/01/30/business/30spine.html>. The N.Y. TIMES reports that one participant in the Prodisc clinical trials brought suit, alleging that her surgeon “seemed more concerned with the prospects for the Prodisc than for her medical care.” The suit was settled in 2007.
- ¹⁹³ Press Release, Synthes, *Synthes Settles with New Jersey Attorney General and Agrees to Reimburse Investigation Costs of US \$236,000* (May 5, 2009), [http://www.synthes.com/html/News-Details.8013.0.html?&tx_synthesnewsbyxml_pi1\[showUid\]=22](http://www.synthes.com/html/News-Details.8013.0.html?&tx_synthesnewsbyxml_pi1[showUid]=22).
- ¹⁹⁴ Notably, the Agreement explicitly permits “financial incentives directed solely at patient accrual or patient follow-up” and fails to require that physician-investigators disclose such incentives to research participants. This does not mean, of course, that the IRB or conflict of interest committee might not require disclosure of these financial incentives. The Agreement makes no mention of a conflict of interest committee and appears to assume that responsibility for managing conflicts will rest with the IRB. *Assurance of Voluntary Compliance*, *supra* note 5, at Section C, Part 9.
- ¹⁹⁵ *Id.* at Section C, Part 1(d).
- ¹⁹⁶ Jon Kamp, *New Jersey’s AG Issued Subpoena to J&J’s DePuy Unit in May*, WALL ST. J., Aug. 4, 2009, available at <http://online.wsj.com/article/SB124942513406505943.html>.
- ¹⁹⁷ Indictment, U.S. v. Biovail Pharm., Inc. (D. Mass. 2008); U.S. v. Biovail Pharm., No. 08-cr-10124-NG (D. Mass., sentencing announced 9/14/09); *New Jersey Company Agrees to Plead Guilty to Kickbacks and Conspiracy Charges and Pay More Than \$22 Million Dollars in Criminal Fine*, *supra* note 6.
- ¹⁹⁸ See Robertson v. McGee, 2002 U.S. Dist. LEXIS 4072, at *9 (N.D. Okla. Jan. 28, 2002) (suit against hospital, principal investigator, pharmaceutical sponsor, a top university official, members of the IRB, and university bioethicist for deaths occurring during Phase I trial of a cancer vaccine; the court held that there is no private right of action for violation of the federal regulations governing human subjects research).
- ¹⁹⁹ 269 F. Supp. 2d 1286, 1291 (W.D. Wa. 2002).
- ²⁰⁰ *Id.* at 1286; see also Duff Wilson & David Heath, *The Blood Cancer Experiment: Patients Never Knew the Full Danger of Trial They Staked Their Lives On*, SEATTLE TIMES, 2001, available at http://seattletimes.nwsourc.com/uninformed_consent/bloodcancer/story1.html.
- ²⁰¹ Wilson & Heath, *supra* note 200. The Hutch denied the reporters’ allegations and there were complaints that the reporting was biased. See *Q & A on This Series*, SEATTLE TIMES, Mar. 25, 2001, available at http://seattletimes.nwsourc.com/uninformed_consent/qa.html.
- ²⁰² Specifically, the court rejected the claim that by withholding information the defendants violated the trial participants’ rights under the federal human subjects protection regulations, and their rights as third-party beneficiaries of the Hutch’s Federalwide Assurance, a written assurance of compliance with the human subjects protection regulations which institutions engaged in research conducted or supported by HHS must execute.
- ²⁰³ David Heath & Luke Timmerman, *Jury Finds Hutch Not Negligent in 4 Deaths*, SEATTLE TIMES, April 9, 2004, available at <http://www.irbforum.org/forum/read/2/72/72?PHPSESSID=b3bdb530bcef550518ee9b3f48f4ae7d>.
- ²⁰⁴ *Id.*
- ²⁰⁵ *Id.*
- ²⁰⁶ Complaint, Darke v. Isner, No. 02-2194-E (Mass. Super. Ct. Aug. 2, 2002).
- ²⁰⁷ Darke v. Isner, No. 02-2194-E, 2004 Mass. Super. LEXIS 250, at *3 (Mass. Super. Ct. 2004).

- 208 Complaint, *Darke v. Isner*.
- 209 *Darke*, 2004 Mass. Super. LEXIS 250 at *4-10.
- 210 Dr. Isner passed away in October 2001.
- 211 *Darke v. Isner*, No. 02-2194-E, 2005 Mass. Super. LEXIS 663, at *15-17 (Mass. Super. Ct. 2005). The court also denied the Isner Estate's motion for summary judgment on Darke's negligence/wrongful death claim, finding that enough evidence was presented to demonstrate that a doctor-patient relationship existed, and also denied the Estate's motion to dismiss Darke's intentional infliction of emotional distress claim. The court granted the Estate's intentional battery and breach of contract summary judgment motions.
- 212 *Id.* at 22-25. Although the deceit and gross negligence claims survived summary judgment, it appears from the docket and from the verdict that the jury ultimately dismissed these claims on the merits. Jury Verdict, *Darke v. Isner*, No. 02-2194-E, 2007 WL 2219825 (Mass. Super. Ct. May 4, 2007).
- 213 Complaint, *Gelsinger v. Trustees of the Univ. of Pa.*
- 214 *Id.*
- 215 David Resnik, *Disclosing Conflicts of Interest to Research Subjects: An Ethical and Legal Analysis*, 11 ACCOUNTABILITY IN RESEARCH 141, 142 (2004).
- 216 *Settlement is Reached in Fatal Experiment*, N.Y. TIMES, Feb. 10, 2005, available at <http://query.nytimes.com/gst/fullpage.html?res=9F0DE2D6163AF933A25751C0A9639C8B63>.
- 217 Gerald R. Prettyman, Jr., *Ethical Reforms in Biotechnology Research Regulations*, 15 VA. J. SOC. POL'Y & L. 51, 69 (2007).
- 218 Studies and compensation models that are motivated primarily by product promotion and not a need for scientific inquiry or that are unlikely to produce useful data do not qualify as research and are therefore ethically unjustifiable and should never occur.
- 219 This risk is real. Internet research reveals several articles directed to a physician audience purporting to outline for physicians how to take advantage of the lucrative opportunities available by running clinical trials out of their private practices. See, e.g., *Clinical Trials May Represent a Business Opportunity*, PHYSICIAN COMP. REPORT (Aug. 23, 2000), http://findarticles.com/p/articles/mi_m0FBW/is_13_1/ai_64777380/.
- 220 See Section III.B.1, *supra*.
- 221 See Boyd, *supra* note 45, at 207.
- 222 See Dana & Loewenstein, *supra* note 115, at 254.
- 223 See Section III.A.5 *supra*.
- 224 See, Richard A. Romero, *Fair Market Value: Taking a Proactive Approach*, 62 HEALTHCARE FIN. MANAGEMENT 88, 90 (2008) (discussing "three possible approaches that can be used to determine fair market value: the cost approach, the market approach, and the income approach.").
- 225 See *supra* note 38 and accompanying text.
- 226 Ferrari, *supra* note 178, at 11 (listing criteria to consider, including the physician's educational credentials, specialized training, professional certifications, leadership experience, and academic appointments and the specific responsibilities and expected time commitment involved).
- 227 See Section II.B.5, *supra*.
- 228 Friedman, *supra* note 80, at 275.
- 229 See Sections II.B.5 and III.A.4, *supra*.

Conflicts of Interest in Clinical Trial Recruitment & Enrollment

- ²³⁰ This is distinct from but raises issues similar to circumstances where investigators and institutions hold more than a de minimis equity stake or patent or other intellectual property interest that could be affected by research they are considering conducting. This situation is discussed in Section IV.C.2.
- ²³¹ The Public Health Service regulations on investigator conflicts of interest promulgated in 1995 define a person covered by the regulations as any investigator involved in designing, conducting or reporting on funded research, as well as the investigator's spouse and dependent children. 42 C.F.R. § 50.603.
- ²³² See AAMC-AAU 2008 COI Report, *supra* note 2, at 6; IOM Report, *supra* note 2, at S-14.
- ²³³ As proposed by IOM, this exception should exist “only if the conflict of interest committee (a) determines that an individual’s participation is essential for the conduct of the research and (b) establishes an effective mechanism for managing the conflict and protecting the integrity of the research.” IOM REPORT, *supra* note 2, at 4-17.
- ²³⁴ See Section II.C.1, *supra*.
- ²³⁵ See PROMOTION WHITE PAPER, *supra* note 1, at 1.
- ²³⁶ See Responsibility of Applicants for Promoting Objectivity in Research for Which Public Health Service Funding Is Sought and Responsible Prospective Contractors; Request for Comments, *supra* note 134.
- ²³⁷ 45 CFR § 46.107 (e) (2009).
- ²³⁸ IOM REPORT, *supra* note 2, at 8-1-8-11.
- ²³⁹ See Section II.A.7, *supra*.
- ²⁴⁰ For a discussion of the characteristics, advantages, and disadvantages of independent IRBs, see COLEMAN ET AL., *supra* note 122, at 197-201; Lis & Murray, *supra* note 47, at 84-90.
- ²⁴¹ See Kevin P. Weinfurt et al., *Disclosure of Financial Relationships to Participants in Clinical Research*, 361 NEW ENGL. J. MED. 916, 919-920 (2009). The AAMC also supports such a practice. See AAMC-AAU 2008 COI REPORT, *supra* note 2, at 26.
- ²⁴² See Section II.C.3, *supra*.
- ²⁴³ See *id.*

APPENDICES**Appendix A****Summary of March 23 Forum on
Enrollment and Recruitment into Clinical Trials**

On March 23, 2009, the Center for Health & Pharmaceutical Law & Policy at Seton Hall Law School hosted a Forum to address the ethical, legal and policy issues posed by recruitment and enrollment of human subjects into clinical research. Entitled, *Protecting Participants, Advancing Science: An Agenda for Reform of Clinical Research Recruitment and Enrollment*, the Forum brought together leaders from academic medicine, industry, academia, consumer organizations, legal and ethics experts and government representatives. The goal of the Forum was to inform the Center's work on articles and white papers laying out recommendations for public policy and institutional practices to enhance protection for research participants and the scientific integrity of clinical research.

The Forum began with a presentation by Carl Coleman, J.D., Professor of Law, Seton Hall University School of Law, on "The Legal Framework for Recruitment and Enrollment," in which he described the current state of federal regulation of human subjects recruitment. Tracy Miller, J.D., Executive Director of the Center for Health & Pharmaceutical Law & Policy presented a summary of key empirical evidence related to disclosure of physician financial incentives to prospective research participants, entitled "Physician Financial Incentives: What do the Data Show?" Following these presentations, the participants covered several key topics posed by recruitment and enrollment of human subjects into clinical research: (i) physician-investigator payments and recruitment incentives, including finder's fees, recruitment and retention bonuses, and per capita payments and the implications of such payments for the interests of participants; (ii) disclosure of compensation for research and other financial interests of investigators and institutions to participants in research, and to IRBs; and (iii) financial incentives for participants in research. On each topic, the Forum participants shared their diverse perspectives and expertise, and explored common ground for concrete, practical solutions to advance the protections accorded participants in clinical trials.

On the first topic, many of the Forum participants noted that bonuses for recruitment and retention are problematic; some questioned how widely used they are at this time. In terms of finder's fees for referring individuals into a study, a clear distinction was made between fair market value compensation for time spent screening and educating patients about the study and payment solely for a referral which should not be acceptable. Widespread agreement supported per capita payments, with some participants recognizing the lack of a clear methodology for such payments, especially outside the context of academic medicine.

On the topic of disclosing financial interests to participants in research, the Forum participants expressed a range of views. For example, some expressed the opinion that disclosure might further complicate an already complex informed consent process. Others advocated far more explicit disclosure than has occurred to date, arguing that participants in practice and in studies conducted on attitudes about disclosure have not been given the information that is most salient – information about the magnitude or amount of the compensation paid. Some thought potential participants would not have a context to understand this information. Overall,

the discussion recognized that disclosure by itself is not an adequate response to conflicts of interest, but must be paired with enhanced oversight by government, including clearer policy guidance for the obligations of institutions to identify and manage conflicts of interest.

Addressing the issue of incentives and payment for human subjects in clinical trials, many of the Forum participants agreed that the prevailing regulatory framework which prohibits any compensation that would unduly influence the decision to enter a trial, is unrealistic and unfair to clinical trials participants. Overall, many participants urged that the existing regulatory framework should be revisited and reformulated. Researchers, employees of the sponsor, and others who are part of the chain leading up to and conducting the trial are all paid for their participation. Those who enroll should be paid as well for their time, inconvenience, and discomfort. However, on this latter point, several of the participants noted the dilemma of paying for discomfort and risk, because while it is the reality of how patients are recruited to undertake certain studies, higher payment for greater risks may also be an inducement for lower income or more vulnerable individuals to undertake risks that may result in harm, without the prospect of reimbursement by the sponsor or the entity conducting the research.

Participants at the Forum on Enrollment and Recruitment into Clinical Trials

Gary Budney, BS, Senior Director Compliance & Business Practices,
Schering-Plough Corporation

Cathryn Clary, MD, Vice President U.S. External Medical Affairs, Pfizer Inc.

Nancy Dubler, LLB, Consultant for Ethics New York City Health and Hospitals Corporation
and Senior Associate, Montefiore-Einstein Center for Bioethics

Susan H. Ehringhaus, JD, Associate General Counsel, Regulatory Counsel,
Association of American Medical Colleges

Terry Fadem, MS, Managing Director, Corporate Alliances,
University of Pennsylvania School of Medicine

Felix A. Khin-Maung-Gyi, PharmaD, MBA, CEO, Chesapeake Research Review

Arthur Levin, MPH, Director, Center for Medical Consumers

Jerry Menikoff, MD, JD, Director, Office of Human Research Protections,
U.S. Department of Health & Human Services

Mary Monovoukas, JD, Senior Director, Corporate Counsel, Boston Scientific Corporation

Lori Queisser, BS, Senior Vice President Global Compliance & Business Practices,
Schering-Plough Corporation

Denise V. Rodgers, MD, Provost & Executive Vice President,
University of Medicine & Dentistry of New Jersey

Adil Shamoo, PhD, Professor, University of Maryland School of Medicine,
Co-Founder, CIRCARE

Jay P. Siegel, MD, Group President, Research & Development, President,
Centocor Research & Development, Johnson & Johnson

Jeffrey H. Silverstein, MD, Professor, Vice Chair for Research, Department of
Anesthesiology, Mount Sinai School of Medicine

Marjorie Speers, PhD, President & CEO, AAHRPP

David H. Strauss, MD, Professor & Director, Office of Human Subjects Research,
Columbia University Medical Center

Michelle Weiner, JD, Deputy Attorney General, Affirmative Litigation Section,
State of New Jersey, Department of Law & Public Safety

Alan Wertheimer, PhD, Senior Research Scholar, Department of Bioethics, Clinical Center,
National Institutes of Health

**Participants from Seton Hall Law School
Center for Health & Pharmaceutical Law & Policy**

Kathleen M. Boozang, JD, LL.M., Associate Dean for Academic Advancement &
Professor of Law

Carl Coleman, JD, Professor of Law & Faculty Director, Center for Health &
Pharmaceutical Law & Policy

Tracy Miller, JD,* Executive Director, Center for Health & Pharmaceutical Law & Policy

Kate Greenwood, JD, Faculty Researcher, Center for Health & Pharmaceutical
Law & Policy

Valerie Gutmann, JD, Faculty Researcher, Center for Health & Pharmaceutical
Law & Policy

* Ms. Miller served as Executive Director through September 4, 2009.

Appendix B

Center for Health & Pharmaceutical Law & Policy

The Center for Health & Pharmaceutical Law & Policy at Seton Hall University Law School advances scholarship and recommendations for public policy on cutting edge issues posed by pharmaceutical and health law. The Center also serves as a forum to convene leaders in government, industry, academia, medicine and consumer organizations to examine the issues posed by clinical and policy developments and explore potential solutions. The Center builds upon the nationally recognized scholarship in health law, conferences on key public policy questions, and an internationally recognized healthcare compliance training program that are part of the Health Law & Policy Program at Seton Hall Law School.

The Center:

- Researches, reviews, and develops policy recommendations on key issues on health and pharmaceutical law to inform and shape policy at the state and national levels;
- Produces scholarship through journal publication and white papers on emerging legal, ethical, and social issues in health and pharmaceutical law;
- Provides a neutral forum to convene leaders in government, industry, academia, and medicine to engage in an informed dialogue, consider pressing policy questions, and explore potential solutions;
- Offers educational programs on health and pharmaceutical issues by leading experts from the public and private sectors to examine important policy and legal issues; and
- Holds compliance education and training programs on state, federal and international regulatory requirements that govern the research, approval, promotion, and sale of drugs and devices.
- The Center operates under the direction of Associate Dean and Professor Kathleen Boozang, Executive Director of Global Healthcare Compliance & Ethics Education Simone Handler-Hutchinson, and Staff. In addition to their expertise in public policy, health and pharmaceutical law, ethical issues in medicine, and healthcare compliance, the Center draws upon the intellectual strength of the Seton Hall Law School faculty. Faculty members bring to the Center's work nationally recognized expertise in pharmaceutical law, not-for-profit governance, intellectual property law and bioethics, among other areas.

Appendix C

Center Financial Disclosure Statement and Policies

The Center for Health & Pharmaceutical Law & Policy of Seton Hall Law School is committed to independent academic inquiry focusing on issues affecting health and pharmaceutical law and policy. As a part of Seton Hall University, the Newark-based Law School is a nonprofit 501(c)(3) organization. The University and Law School engage in fundraising from alumni and other contributors. Remaining committed examining divergent perspectives on policy issues related to health and pharmaceutical law and policy is critical to the mission of the Center.

Law School faculty members and Center Staff are devoted to academic independence in their research and transparency in their relationships. As such, funding sources are announced on all published materials and on the Law School Web site. Regardless of whether financial support is received in the form of an endowment, as unrestricted funds or for a specific project, Law School and Center donors are not involved in the academic work of Law School professors or Center Staff. Grants and donations are only accepted if they do not limit the faculty's or the Center's ability to carry out research free of outside influence and consistent with the Center's mission and values.

Seton Hall Law School funds the salaries of the faculty associated with The Center for Health & Pharmaceutical Law & Policy. Research and administrative support for the Center are jointly funded by Seton Hall Law School and by unrestricted funds provided by corporate donors, with the Law School currently providing the majority of the funding.

The Center for Health & Pharmaceutical Law & Policy and its faculty assume sole responsibility for the content of its publications and position statements. The Center does not issue publications or statements on behalf of any donor or other entity.

The corporate donors that have provided funding to the Center or to the Law School are listed below.

- In 2009, Ernst & Young committed \$25,000 to support the creation of a European healthcare compliance program slated to be implemented in 2010.
- Bristol-Myers Squibb provided a \$5 million endowment in 2005 in support of The Harvey Washington Wiley Chaired Professorship in Corporate Governance & Business Ethics. The Law School is recruiting candidates for this position.
- Johnson & Johnson provided \$100,000 in 2008 as seed funding for two projects (i) a program on Strategies for Compliance Professionals: Honing Decision-Making Skills, and (ii) creation and implementation of an international compliance program. It provided an additional \$50,000 in unrestricted support, also in 2008. In 2007, Ortho-McNeil Janssen Scientific Affairs, a subsidiary of Johnson & Johnson provided \$49,900 in unrestricted funds. Johnson & Johnson provided \$50,000 in 2007 and \$100,000 in 2006 in unrestricted funds to support the Center. Two of Johnson & Johnson's subsidiaries, Centocor, Inc. and Ortho Biotech, provided \$125,000 in unrestricted funding to the Center in 2007.
- In 2006, sanofi-aventis provided \$500,000 to Seton Hall Law School in support and development of the Center for Health & Pharmaceutical Law & Policy and the programs and activities associated with the Center.

Conflicts of Interest in Clinical Trial Recruitment & Enrollment

- In 2006, Schering-Plough Corporation made a \$2.5 million commitment to be paid over five years to partially endow a tenured track/tenured faculty position dedicated to health care regulation. The Law School is currently recruiting candidates for this position in the 2009-2010 academic year.
- In 2008, Purdue Pharma provided \$25,000 in unrestricted funding for the Center for Health & Pharmaceutical Law & Policy.
- In 2008, Roche provided \$50,000 for a symposium sponsored by the Gibbons Institute of Law, Science & Technology, the Seton Hall Law Review, and the Center on Preparing for a Pharmaceutical Response to Pandemic Influenza.

For further information about
Programs and publications of
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please visit our website at *law.shu.edu*

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