

## **Institutional Financial Conflicts of Interest in Clinical Research**

**By Robert S. Bienkowski and Norman M. Goldfarb**

### **Introduction**

Two government actions in the 1980s have had far-reaching implications for clinical research:

- The Bayh-Dole Act of 1980 allowed institutions to retain ownership rights to intellectual property created with support of government funds and to negotiate royalty-bearing licensing agreements. It also required institutions to share proceeds of licensing agreements with faculty inventors. Bayh-Dole has provided the impetus for converting academic inventions into practical uses for the benefit of the public.
- Regulations issued in 1981 by the Department of Health and Human Services (DHHS) and its agency, the Food and Drug Administration (FDA), codified requirements for protecting human subjects in biomedical research.

The entrepreneurial activities encouraged by Bayh-Dole have created ethical issues not explicitly covered by the regulations for protecting human subjects in research. Individual and institutional conflicts of interest (COIs) can result when product development requires clinical trials with human subjects, and individual inventors and their institutions have financial interests in the outcomes of the trials.

A financial conflict of interest in clinical research requires three elements:

- The person or institution must have an interest in the financial implications of a clinical trial.
- The person or institution must play a role in designing, conducting, analyzing or publishing the findings of the clinical trial.
- The person or institution must have a duty of care for the participants in the clinical trial.

The third element applies to all clinical research sites and their personnel, but is especially important for institutions like hospitals and clinics that enroll their own patients in clinical studies. These institutions have dual duties of care to people who are both patients and study subjects.

A financial stake in research can often be traced to an institution's ownership of intellectual property developed with federal funds. When successful, the institution licenses its intellectual property, for example a patent, to a commercial entity, which takes responsibility for developing and marketing commercial products based on the intellectual property. Royalties on sales of the products flow back to the institution, which then shares the income with the inventors. The institution may also obtain equity (stock), grants and other financial benefits from the relationship.

Whereas individual COIs have been discussed widely and almost all institutions have policies to deal with them, institutional COIs have been less appreciated as a problem for clinical research. Institutional COIs rarely occur without a corresponding individual conflict and create special challenges, as will be discussed below.

An important characteristic of COIs is that it can be impossible determine what, if any, inappropriate decisions or conduct they cause. Institutional policies thus focus on the possibility that they might cause problems, as a precautionary measure.

## High-Profile Cases of Institutional COI in Clinical Research

The following high-profile cases illustrate various types of institutional COI:

### Development of Intellectual Property

A clinical trial at the University of Pennsylvania in 1999 offers an especially dramatic illustration of the consequences of not managing individual and institutional financial COIs.<sup>1,2</sup> Jesse Gelsinger, a 17-year-old boy with a mild case of ornithine decarboxylase (ODC) deficiency, volunteered to participate in a gene transfer experiment at Penn. He died as a result of a massive immune response to a virus that had been engineered to carry a genetic sequence coding for ODC. Dr. James Wilson (the inventor of the technology), Penn and Biogen (a biotechnology company) were especially creative in how they structured their financial interests. Wilson had previously created a company, Genovo, which was now owned by Wilson, Penn, Biogen and other shareholders. The University formed a new Institute for Human Gene Therapy (IHGT), which Genovo funded with \$21 million. IHGT funded the ODC clinical trial. Wilson was a tenured professor at Penn, performed services for Genovo, was the director of IHGT, and participated in the ODC clinical trial as co-investigator.<sup>2</sup>

Paul Gelsinger, Jesse's father, brought suit against Wilson, Penn, Genovo and others, claiming, in part, that their financial interests had not been adequately disclosed during the informed consent process. The parties eventually settled the case out of court for an undisclosed amount, and the FDA sanctioned Wilson. It is not known whether the conflicts of interest directly contributed to the tragic results, but they certainly did not protect Jesse.

### Support for Capital Projects

During the 1990s, Dr. Nancy Olivieri conducted studies on a new drug to reduce iron load in thalassemia patients at the Hospital for Sick Children (HSC) in Toronto, Canada.<sup>3</sup> HSC is a teaching hospital for the Faculty of Medicine of the University of Toronto. Staff physicians hold faculty appointments at the University but are not employed by it. Apotex, a pharmaceutical firm, sponsored Olivieri's studies and also employed her as a consultant at the same time. Apotex had made a sizeable donation to the University to construct a research center and was discussing possible donations to HSC.

Olivieri became convinced that the drug was ineffective for some of her study subjects and wanted to make her findings public, but Apotex was not persuaded by Olivieri's data and invoked a contract clause that gave it editorial control over what she could disclose. A legal battle ensued. Olivieri claimed that neither HSC nor the University had supported her right to publish her findings. The four-way dispute involving the investigator, HSC, the University, and Apotex was a long-running story in the Canadian press, as well as in commentaries in international scientific journals. Although Olivieri has received numerous honors from universities and professional organizations that cite her courageous stand for scientific integrity and academic freedom, nobody won this battle.

### Rainmakers

Physicians who generate substantial revenue for healthcare institutions can gain influence over the institutions' decision-making processes. While the problem is readily apparent in clinical activities involving procedures, it also appears in clinical research in the form of grants and contracts that cover not only direct costs but also overhead income for the institution. Clinical research generates a financial COI when, for example, a physician wants to conduct a clinical trial that may be advantageous to the physician and institution, but not so much to the patients. Academic psychiatry appears to be especially active at the nexus of personal and institutional conflicts of interest with Nemeroff at Emory, Biederman at

Massachusetts General Hospital, and Schatzberg at Stanford being among the highest profile cases.<sup>5-7</sup>

### **Endowed Chairs**

Dr. Charles Nemeroff, former chairman of Psychiatry at Emory University, received hundreds of thousands of dollars in consulting and speaking fees from drug manufacturers between 2000 and 2007, while he was conducting NIH-funded research on drugs manufactured by the companies for which he was consulting. Senator Chuck Grassley expressed serious concerns about Nemeroff's COIs and demanded that the Inspector General of DHHS investigate the matter.<sup>5</sup> In a letter to the Dean of the Emory School of Medicine, Nemeroff cited his ability to attract industry funding for endowed chairs as justification for his close relations with the companies,<sup>8</sup> and that inducement qualifies this case as a potential institutional COI.

### **Financial Interests of Senior Administrators**

Senior institutional officials can have personal financial interests in entities that sponsor research at their institutions. For example, Dr. Delos Cosgrove, CEO of Cleveland Clinic, developed a device to treat atrial fibrillation. He sat on the board of directors of the company that manufactured the device and sponsored clinical trials of it at the Clinic. He was also a general partner in a venture capital fund that provided financial support for the company.<sup>9</sup>

### **Inherent Institutional COI**

A common element in these examples is that specific persons figure prominently in each conflict. Another common feature is the large amount of money involved in each case, suggesting that such COIs may be limited to major research institutions. These conflicts can be managed and perhaps avoided by a robust set of policies and procedures for disclosing and evaluating financial interests. And, indeed, the institutions mentioned have all developed such policies.

There is, however, an institutional COI that is *inherent* in clinical research, that does not feature specific persons, and that does not depend on institutional size. It arises whenever a healthcare institution becomes an investigative site for industry-sponsored clinical trials. Upon executing a clinical research agreement, an institution assumes a business obligation to a customer, the study sponsor, and it is presented with financial incentives to convert patients into study subjects.

A clinical trial fundamentally changes the relationship between institution and individual: The patient-clinic relationship now co-exists with a research subject-research site relationship. This duality is most problematic when a treating physician enrolls his or her own patient in a clinical trial. This is not to say that such patients do not benefit from participation in the clinical trials, only that a financial COI can influence the interaction. Ironically, disclosing the investigator's and institution's financial interests in a clinical trial may assure a potential subject that the trial is legitimate.<sup>11</sup>

Problems can arise when the patient/subject and the clinic/research site misunderstand the position of the other party in a given interaction. These interactions, which can contribute to the therapeutic misconception, can be called "inappropriate" because they can mask the underlying COI.<sup>11</sup> For example, in a therapeutic misconception, the patient/subject can accept as medical care what the clinic/research site is offering as research participation.

Institutions can minimize the probability of a patient/subject misunderstanding the institution's role with the following measures:

- Training personnel to clearly state their role in each patient/subject interaction.
- Explaining the dual relationships during the informed consent process.
- Having someone other than the patient's physician obtain informed consent for a clinical trial, or at least have a significant role in the process.

All financial aspects of a person's participation in a clinical trial, be it a stipend for travel or charges for research-related testing, should be clearly distinguished from financial transactions involving the person's healthcare.<sup>12</sup> This differentiation can be difficult with billing systems that manage charges to the patient, third-party payors like Medicare and insurance companies, study sponsors, and the institution itself. For better or worse, Medicare is playing an active role in assuring that billing systems operate correctly.

### **Managing Institutional COIs in Clinical Research**

As already noted, most major research universities have developed policies and procedures to handle the situations that can lead to high-profile institutional COIs. Many of these policies are based on a model created by the Association of American Medical Colleges and the Association of American Universities.<sup>13</sup> Research administrators at small institutions might think that they don't need such extensive policies, and perhaps they're right. However, they might consider adopting the simple policy developed by Boyer et al in case the need arises.<sup>14</sup> Huron Consulting Group has published a policy that covers the important points in less than one page.<sup>15</sup> In contrast, inherent COI is best managed by human subjects protection policies and procedures.

Disclosure, evaluation and development of a management plan are the required elements of any policy on financial COIs. Managing the high-profile type of institutional COIs is challenging because the financial stakes are typically larger, the politics can be more sensitive, and the institution is essentially policing itself. The authority and objectivity of the institutional COI committee are subject to question. Participants in the committee can find their roles uncomfortable. The committee is probably inexperienced because the high-profile type of institutional COIs is uncommon. The committee's inquiries usually require information that is private, proprietary and sensitive. Effective institutional COI committees thus require dedication, independence and support from senior management. The work of the institutional COI committee is certainly easier if potential conflicts are brought to its attention before they create problems.

Managing inherent COIs is challenging because they involve numerous people and cannot be avoided, only mitigated with policies, procedures, training programs, and constant vigilance.

### **Conclusion**

Healthcare institutions should consider the cases discussed above and ask two questions: Can they happen at our institution? If so, are our institutional COI and human subjects protection policies and procedures adequate?

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