

INSTITUTIONAL CONFLICTS OF INTEREST

Identifying and Managing Them in Life Sciences

by Eric Hargan

Elimination of unanticipated or unknown conflicts of interest related to clinical research in the life sciences is critical for any device or drug being developed in today's environment. Recent reports and activity by the media, the courts, advocacy groups, trade associations and even Congress have placed conflicts of interest squarely in the spotlight for device manufacturers, researchers and institutions involved in clinical research.¹ Recently, for example, manufacturers of the Prodisc artificial spinal disk were revealed to have financial ties to investigator physicians at nearly half of the research institutions involved in clinical studies of the disk's effectiveness,² which resulted in denial of coverage by payors, private lawsuits and the launching of an investigation by Senator Charles Grassley of the Senate Finance Committee.³

A study conducted by Duke University Medical Center and Johns Hopkins University reported in 2007 that only 41 percent of clinical trial coordinators surveyed had experience disclosing financial aspects of the trial to potential participants and that 28 percent of the coordinators had been asked by participants about potential financial conflicts.⁴ The stakes are high: \$95 billion in medical research spending was

reported in 2005, of which 57 percent is industry sponsored,⁵ and in the device industry, an extremely high proportion of research is front-end R&D investment. With high stakes and growing official and public interest in this area,⁶ a comprehensive method for companies and institutions to identify and manage their institutional conflicts of interest (Institutional COI) has become an essential element of any comprehensive risk management program related to clinical research.

"Conflicts of Interest" are defined by the Association of American Medical Colleges (AAMC) and the Association of American Universities (AAU) as "situations in which financial considerations may compromise, or have the appearance of compromising, an investigator's professional judgment in conducting or reporting research."⁷ As identified by the AAMC, conflicts of interest can exist at both the individual and institutional levels,⁸ and both types of conflicts must be addressed. In this article, we address Institutional COI, defined by the AAMC Report (in a definition similar to others) as "conflicts of interest based on either the financial interests of the institution itself or of its officials acting in leadership or supervisory positions."⁹

Institutional COI can arise from financial or associational interests held either by the entity itself or by individuals (Key Officials) within the entity who have decision-making authority regarding clinical research. Examples include: donations by industry to research organizations; investment by a research organization in the product it is testing; or stock holdings by Key Officials of a research organization in a company licensing a product tested by the organization. Suffice to say that these conflicts are pervasive. A failure by institutions or companies to properly assess these risks can have dire consequences. And although individual conflicts of interest may be, and are often, contracted around by the use of standard disclosure provisions and documents, certain Institutional COI—in particular, the appearance of Institutional COI—cannot be contracted around. It is important to remember that these types of COI are not likely to be resolved with boilerplate



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language. All parties involved are, and remain, at risk.

Furthermore, compounding the difficulty, the informational coordination complexities inherent to Institutional COI mean that risk-shifting is not practical; instead, as we explain below, risk management through appropriate due diligence is the best goal for institutions and companies. This article identifies the current regulatory landscape relating to Institutional COI, identifies risks associated with unknown or unanticipated Institutional COI, identifies the proper parties empowered to address them, and sets forth practical steps that parties may implement to minimize their impact.

Current Regulatory Environment

The clinical research realm is, in a sense, very comfortable with the laws and regulations addressing individual conflicts of interest. Indeed, many research institutions go beyond legal requirements and institute conflict of interest requirements that are even more stringent than legally required. And this is logical, because much of the current focus in conflicts of interest is on individual conflicts of interest. For example, Public Health Service (PHS) regulations include requirements that most research funded by PHS grants or cooperative agreements have in place written conflict of interest policies;¹⁰ that investigators must disclose certain “Significant Financial Interests” to the institution;¹¹ and that institutions report to the PHS the identification of the conflict and provide assurances of management, reduction or elimination of it.¹² The Food and Drug Administration (FDA) regulations require disclosure of certain financial relationships between the study sponsor and

study investigators after completion of a clinical study (though FDA regulations are very broad),¹³ and Section 701 of the Food and Drug Administration Amendments Act of 2007 mandates that FDA advisory committee members who are full-time Government employees or special Government employees must disclose certain financial interests.¹⁴

Happily, recent reports have shown that adoption of individual conflict of interest policies has achieved a high level of compliance within the research industry. For example, in 2004, a report by the AAMC and AAU revealed that 98 percent of responding U.S. medical schools had adopted definitions of “significant financial interest” or some similar concept in their policies, and concluded that “[t]he study results provide clear evidence of substantial responsiveness . . . in strengthening their conflict of interest policies well beyond the minimum federal standards in recognition of the markedly changed circumstances of clinical research.”¹⁵

Institutional COI, on the other hand, are not afforded a similar degree of official guidance, and policies addressing such conflicts are not yet uniformly adopted. The Department of Health and Human Services Financial Relationships Guidance, published in May 2004, includes a recommendation that institutions establish a committee to address institutional conflicts of interest (as well as individual ones), independent of the Institutional Review Board (IRB) of the institution.¹⁶ However, the lack of attention to this area has led to slow implementation of controls. For example, a study published in the February 18, 2008, issue of the *Journal of the American Medical Association* reported that only 38 percent of academic medical centers in the United States reported

having an Institutional COI policy; 37 percent are working on adopting a policy; and 25 percent reported that they were not working on such a policy or do not know.¹⁷ Thus, a majority of academic medical centers do *not* have an Institutional COI policy.

Good numbers do not exist for how many research entities, broadly speaking, have such policies. However, managing Institutional COI should be a top priority, and it should not be assumed that mere compliance with legal requirements relating to conflicts of interest will sufficiently address Institutional COI; parties should extend the reach of their policies and procedures beyond the minimum legal requirements due to the risks illustrated below.

What Are the Risks with Institutional COIs?

Failure to identify and manage Institutional COI may lead to a variety of potential negative consequences. An Institutional COI, especially in today’s environment of increased attention to device safety, can lead to rejection of the new device, drug or application by the FDA based on tainted results, a rejection which could cost millions of dollars and years of lost effort;¹⁸ rejection and/or retraction of study results from scientific journals;¹⁹ reduced product sales and/or a public perception of inferiority or risk relative to competitive products; a reluctance of payors to include the device in coverage; potential liability from multiple sources that include: stockholders, study participants and plaintiffs asserting product liability or False Claims Act liability; and increased scrutiny from media and regulators now and in the future. Most importantly, however, is the negative reputational impact, a “taint” of untrustworthiness, that can remain with an involved party

when an Institutional COI is left unresolved or undiscovered, an effect that can be devastating to device manufacturers and institutions in particular.

The media is always interested in these conflicts; and in today's world, even a single article is more or less eternal, due to internet search engines. In such an environment, it is incumbent on individuals and organizations to incorporate "conflicts thinking" into their daily lives and routines. The fact that the mere appearance of such a conflict has such harsh reputational impacts is of particular importance to the life sciences/device world due to the high R&D investment and the high concentration of invested resources in a small number of products.

In 2000, the parents of Jesse Gelsing, an 18-year-old subject in a gene therapy clinical trial who passed away in the course of the study, filed a lawsuit against a large well-regarded university, alleging in part that there was a failure by the university to disclose the fact that the principal investigator had a financial relationship with the sponsor of the trial, which resulted in a settlement for an undisclosed amount, in addition to over \$500,000 in fines and enhanced oversight conditions on the university by governmental sanctions.²⁰ More recently, in 2006, it was discovered that a blood filtering device maker had made contributions to investigators in the form of stock as well as contributions to the research foundation that oversaw the study: nearly \$180,000 in 2004 alone.²¹ FDA investigated the research foundation, and the media attacked, which will no doubt lead to a harder look at future research results from everyone involved. Finally, as recently as Feb. 21, 2008, the amended complaint in

the Prodisc product liability lawsuit filed in the U.S. District Court for the Southern District of Texas includes a claim that the device maker, manufacturer and investment firm intentionally concealed conflicts of interest with participating physician investigators.²² These examples illustrate situations where a comprehensive set of conflicts policies and procedures could have identified and addressed the conflicts prior to study initiation and avoided these consequences. These examples also highlight that all parties, including investigators, non-profit research institutions, and industry entities, have exposure to risk from Institutional COI.

Who Should Bear Responsibility?

Clinical research studies involve multiple parties, all of which have varying interests, as well as different degrees of access to information relevant to identifying Institutional COI. First, governmental entities have theoretically unlimited access to information and a high degree of interest, which would seem to make the government an ideal party to bear responsibility for monitoring Institutional COI. Indeed, governments already do investigate, but short of a government nationalization of the healthcare sector, government will never take responsibility for breaches and will not manage conflicts of interest, but only investigate and enforce. Second, principal investigators are at risk, but they are unable to access or coordinate all of the relevant information, as they have no knowledge of the activities of the institution or company. Third, IRBs also have little access to this information, as it is not required to be reported to IRBs, and the primary interest of the IRB is (and

will no doubt remain) the research protocol and its scientific value and protections afforded to subjects, rather than financial relationships outside of the study itself. IRBs are simply too fragile a vessel to handle this kind of information gathering, coordination and reporting. Finally, companies, such as device manufacturers, and institutions, such as academic medical centers and other research sites, have access to the information because they are the organizations that enter into the relationships; they also have a high degree of interest, because the product as well as the reputations of the institution and industry entity are at risk.

It is crucial, therefore, for both companies and research institutions to be actively involved in the identification and management of Institutional COI in order for the process to operate effectively, as each party's interests are not adequately addressed by the other parties in many cases. This is particularly true in circumstances involving mixed non-profit and for-profit interests, such as a clinical research study involving a not-for-profit research site and a for-profit device manufacturer sponsor.

How Can the Problem Be Addressed?

Early identification and independent evaluation and resolution of Institutional COI is a key element of a comprehensive Institutional COI plan. Development, implementation and proper maintenance of a plan prior to entering into agreements or relationships with entities related to life sciences research are essential in order to permit sufficient time to address and resolve any potential conflicts that may arise.

An effective plan must include: an independent body of evaluators to make determinations regard-

ing identified conflicts, both of the institutional and individual variety; careful training and implementation in accordance with established policies; a reporting mechanism requiring regular updates for both new financial relationships between the institution and research-related entities as well as for Key Officials; a reporting policy that permits identification of all non-*de minimus* financial interests, as determined by the implementing entity, and creates a rebuttable presumption of a conflict; and a formal definition of relationships that permits consistent evaluation by an uninterested group of evaluators in the form of a committee empowered to address Institutional COI.

The approval of the Institutional COI committee should be required prior to the initiation of any clinical research study, and representations should be made by both institutions and industry entities that Institutional COI have been, and will continue to be, identified and addressed during the course of the study within the clinical trial agreement concerning the study in question. Finally, the Institutional COI committee should be empowered with the authority to impose sanctions as well as potentially halt the progress of any clinical research studies that may already be in progress, or even those that have already terminated, with an express recognition of the safety and privacy of subjects and their identifiable health information involved in any affected studies.

Here are some practical tips on how to identify and manage Institutional COI:

- Get a plan ahead of time—do not wait until it is too late to address

any unknown issues, because the media will;

- Make conflicts questions as specific as possible with regards to requirements and obligations (do not ask broad or general questions that are subject to misinterpretation), and make sure parties are compliant with reporting obligations;
- Require active participation from both institutions and companies and take prompt action with regard to any identified conflicts;
- Keep in mind that individual conflicts from key individuals can be imputed to the organization, so make sure to include reporting responsibilities for individuals with decision-making authority relating to clinical research;
- Consider establishing a centralized universal Conflicts of Interest File to keep all conflicts records, both individual and institutional; and
- Seek to implement a Plan that includes sufficient reporting obligations and independent review controls such that a conflict may only exist without the organization's knowledge only in circumstances where deception has occurred.

Conclusion

Companies and research institutions are the only level of the research enterprise that is responsible, capable and motivated to manage Institutional COI. And the stakes are great: possible loss of reputation; rejection of expensive studies by the FDA; lawsuits; and rejection of products by payors. With most AMCs having or working on an Institutional COI policy, now is the time to act. Industry and public expectations are on the move, and rising. These rising expectations mean that mere conflict management by boil-

erplate is not enough. An institution cannot contract around or shift risks to its reputation. And a good reputation is rock-hard currency in a world in which stories and reports are instant, eternal and universally accessible. Institutions that rise to the challenge of new expectations in managing Institutional COI will thrive. Δ

- 1 See, e.g., Association of American Medical Colleges and the Association of American Universities, *Protecting Patients, Preserving Integrity, Advancing Health: Accelerating the Implementation of COI Policies in Human Subjects Research* (2008) (hereinafter the "AAMC Report").
- 2 See Reed Abelson, *Financial Ties are Cited as Issue in Spine Study*, N.Y. Times (Jan. 30, 2008).
- 3 See, e.g., Reed Abelson, *Senator Queries F.D.A. and Spinal Disk Maker*, N.Y. Times (Feb. 28, 2008).
- 4 News-Medical.net, *Conflict of Interest Notification Study* (Apr. 24, 2007), at <http://www.news-medical.net>.
- 5 Associated Press, *Medical Research Got More Money Over Last Decade*, N.Y. Times (Sept. 21, 2005).
- 6 See e.g., Office of the Inspector General, 2008 Work Plan (identifying as an area worthy of attention "Financial Disclosure Requirements for Clinical Investigators").
- 7 <http://www.aau.edu/research/COI.01.pdf>
- 8 AAMC Report, *supra* note 1 at 2.
- 9 AAMC Report, *supra* note 1 at 13.
- 10 42 C.F.R. § 50.604(a).
- 11 42 C.F.R. §§ 50.603, 50.604(c).
- 12 42 C.F.R. § 50.604(g)(2).
- 13 See FDA Form 3455; 21 C.F.R. § 54.2.
- 14 Food and Drug Administration Amendments Act of 2007 § 701, Pub. L. No. 110-85 (September 27, 2007).
- 15 <http://www.aamc.org/research/coi/coireresults2003.pdf> at 5.
- 16 Department of Health and Human Services, *Financial Relationships and Interests in Research Involving Human Subjects: Guidance for Human Subject Protection*, 69 Fed. Reg. 26393 (May 12, 2004).
- 17 Susan H. Ehringhaus et al., *Responses of Medical Schools to Institutional Conflicts of Interest*, 299 JAMA 665-71.
- 18 See 21 C.F.R. § 54.5(c).
- 19 See, e.g., Medical News Today, *MMR Autism Link 10 Doctors Retract* (Mar. 3, 2004), at <http://www.medicalnewstoday.com/articles/6308.php> (retracting data results of an autism study, stating that "[t]he editor of The Lancet said a month ago that he would not have published the findings five years ago if he had known about a lead researcher's fatal conflict of interest").
- 20 Sheryl Gay Stolberg, *Teenager's Death is Shaking Up Field of Human Gene-Therapy Experiments*, N.Y. Times (Jan. 27, 2000).
- 21 See Reed Abelson, *Charities Tied to Doctors Get Drug Industry Gift*, N.Y. Times (June 28, 2006).
- 22 Erin Marie Daly, *Prodisc Patient Widens Circle of Blame*, Health Law 360 (Feb. 28, 2008), at <http://health.law360.com>.