

**CASE AND COMMENTARY: PEER-REVIEWED ARTICLE**

**What Should Physician-Researchers Tell Patient-Subjects About Their Relationships With Industry?**

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**Abstract**

An investigator's personal financial interest in technology under investigation or in the company sponsoring the research is a clear conflict of interest (COI). Such financial relationships are common, and ethical questions rightly emerge about COIs' capacity to compromise an investigator's approaches to research. This commentary on a case suggests that COI disclosure is appropriate during the process of facilitating patient-subjects' informed consent because it promotes informed decision making and motivates transparency. But COI disclosures are not always efficacious, nor are they sufficient to address the problem of research bias. This commentary argues that mitigation or elimination of COIs is a more effective strategy than disclosure.

**Case**

Dr M is a senior resident physician conducting research on a vagal nerve stimulator (VNS) with supervision from the attending physician and principal investigator, Dr A. The VNS was initially approved as a device for a specific indication and application by the US Food and Drug Administration (FDA) following clinical trials. Anecdotal reports from subjects in those clinical trials suggest that VNS might also be helpful for another indication, so the device's manufacturer, Company K, suggested that a novel off-label application of the VNS be investigated by Drs M and A. This new clinical trial is federally funded and also supported financially by Company K. Dr A has received numerous research grants, dinners, and speakers' fees from Company K.

Dr M asks Dr A about the nature and scope of what they need to disclose to subjects during informed consent in order to comply with the Physician Payments Sunshine Act. This law requires manufacturers to report all payments to physicians and for physicians to either confirm or dispute and correct the data within 60 days of it being posted.<sup>1</sup>

"Nothing," responds Dr A to Dr M. "That law applies to manufacturers, not to physicians and patients."

"Well, that's true, but if you were going to enroll in our study, wouldn't you want to know?" Dr M continues.

“I guess I’m not sure what exactly you think patients should be told,” says Dr A. “I mean, how much detail is necessary? In the VNS world, there are a limited number of experts, folks like us, to research new technologies like this device. We have financial ties to these companies because if we don’t, we help these companies for free. So, of course, we have financial ties to these companies. And, of course, we can’t recuse ourselves from decisions affected by ties to these companies because we are the ones best positioned to try to help these subjects, and we are the ones with the expertise needed to take good care of patients who can benefit from new VNS devices. So, Dr M, I do see your concern. I see what you’re saying about disclosure. But when you have limited time with patients, it’s hard to clarify everyone’s interests. I try just to keep things simple when I talk with patients, and I try to keep the focus on what’s at stake for them. If you can think of a better, clearer way for us to be as transparent as we can with our patient-subjects, we can talk about your ideas, but I’ve been doing this for a long time, and this is the best I’ve come up with. Does that help, Dr M?”

“Yes,” says Dr M. Dr M still wonders, however, what their patient-subjects should be told about Dr A’s relationships with Company K before enrolling them in the VNS trial.

### Commentary

A conflict of interest (COI) in this case emerges because Dr A’s professional obligation to objectively conduct research conflicts with her personal interest in the device study generating favorable outcomes. The case asks us to consider what investigators should disclose to patient-subjects during informed consent. Related questions beyond the scope of this article also include whether and which information investigators should disclose to their institutions, sponsors, and journal publishers and readers. In what follows, I argue that investigators, in the case and in general, should **disclose their financial interests** to patient-subjects during informed consent but that medicine, as a profession, should not consider disclosure sufficient for addressing COIs.

### Key Considerations About COIs

It’s helpful first to examine key decisions that COIs can influence and then consider some evidence about whether COIs lead to research bias.

*Decisions, designs.* COIs tend to work through subtle influences on decision making rather than by prompting investigators, say, to deliberately design a biased trial or falsify or fabricate data. But the prospect of money and Dr A’s prior commitments to the company could unconsciously influence many decisions about the trial that favor positive findings for the device. For example, trial design elements that can result in bias include use of a weak comparator drug, inadequate blinding, and poor follow-up.<sup>2</sup>

*Evidence.* Important to note is the absence of strong evidence that investigators’ personal financial interests commonly lead to research bias. Industry sponsorship does not necessarily create COIs, since funding tends to go to investigators’ institutions and might cover a portion of their salary but usually does not augment their income. Yet, it can create COIs when investigators have personal financial interests (ie, stock, speakers fees, royalties) in sponsors’ success. Evidence does show that industry sponsorship is associated with favorable outcomes.<sup>3</sup> While notable from an ethics standpoint, this finding does not imply that investigators’ stakes are the most worrisome sources of bias, since industry roles in study design, data analysis, and data reporting can affect research outcomes. Meta-analyses show that, specifically, investigators’ stock ownership<sup>4</sup> and industry roles<sup>5</sup> in studies are associated with favorable outcomes. We

also know that companies court experts with lucrative payments to be advisors and speakers.<sup>6,7,8</sup> While direct links between investigators' financial interests and study bias is difficult to establish in individual cases, identifying, managing, or eliminating COIs in biomedical research remains a priority for journals and all who are concerned with integrity in research.<sup>8,9</sup>

### Disclosure Requirements

Disclosure to subjects of investigators' financial interests is not required by federal regulations that govern human subjects research and protection. Public Health Service (PHS) regulations encourage consideration of whether to disclose investigator financial interests to participants, but such disclosures are not required.<sup>10</sup> Most academic health centers (AHCs) in the United States have adopted PHS policy about COIs, which requires investigators' disclosure of "significant financial interest[s]" (ie, speaking and consulting fees, stocks exceeding \$5000 over 12 months) to their institutions<sup>11</sup>—but does not require investigators' disclosure of industry ties to subjects—and states that identified COIs must be managed or eliminated.<sup>12</sup> PHS policy also does not stipulate how an institution should manage or eliminate an investigator's identified COIs. COIs are typically addressed by an institutional committee, officer, or institutional review board (IRB); common strategies for managing and eliminating identified COIs include, for example, COI disclosure in publications or requiring data to be analyzed by an investigator without COIs.

In the case, assuming her institution generally follows federal policy for PHS-funded research, Dr A should disclose **diners** and speaking fees to her institution if their value exceeds \$5000 cumulatively during the past 12 months, but she need not disclose grants from Company K to her institution because her institution would, presumably, already be aware of them. Her institution's IRB would determine whether and how Dr A must disclose dinner and fee information to subjects. This determination reflects the general consensus in the research ethics field that investigators should disclose to subjects relevant, significant **financial ties to industry**. The American Medical Association *Code of Medical Ethics* is in accord with this view, stating: "As part of the informed consent process, [investigators should] disclose to prospective participants the nature and source of funding and financial incentives offered to the investigators. This disclosure should be included in any written consent materials."<sup>13</sup> Finally, an influential 2008 joint report on COIs by the Association of American Medical Colleges (AAMC) and the Association of American Universities (AAU)<sup>14</sup> concurs, quoting an earlier AAMC task force report:

[T]he precise wording of disclosure in the consent form should be determined by the IRB, but should include an explanation of the fact that the financial interest in question has been reviewed by the COI committee, approved subject to committee oversight, and determined by both the committee and the IRB not to pose any additional significant risk to the welfare of research subjects or to the integrity of the research.<sup>15</sup>

### Six Goals of Disclosure

Scholars have identified 6 goals of COI disclosures to research subjects.<sup>16,17</sup>

1. *Enable subjects' informed consent and awareness of investigators' stakes.* Research subjects should make informed decisions about their participation in research. This requires awareness of the risks of participation—including factors that can increase risks—and possible benefits and awareness of factors that could threaten a study's integrity.

2. *Protect subjects' right to know about investigators' financial interests.* Some subjects want to know this information even if it is not critical to their decision about whether to participate in a study.<sup>18,19</sup>
3. *Motivate trust.* Disclosure can help establish and maintain subjects' trust in investigators by promoting transparency. This can be key when, during research, subjects become ill or injured, or if they feel manipulated upon learning information they feel should have been revealed earlier.
4. *Minimize legal liability risk.* When, during research, subjects become ill, injured, or otherwise harmed, investigators' conduct prior to an adverse outcome can be important from a **risk management standpoint**.
5. *Deterrence.* Because disclosure can be uncomfortable for investigators, knowledge of an obligation to disclose could deter an investigator from pursuing financial relationships that could generate COIs.
6. *Minimizing risk of harm.* Disclosures might have a protective effect on subjects' welfare by reducing risk to which a subject is exposed over the course of a study.

Investigators' disclosure of financial interests might not always achieve or fully achieve these goals, but each suggests the importance of the role played by the ethical value of transparency and informed decision making for investigators and subjects.<sup>16,20</sup>

### Limits of Disclosure

It is unknown how many AHCs currently disclose investigator COIs to research subjects on a routine basis. In my own experience, disclosure to prospective subjects of investigators' financial interests typically happens during **informed consent**, and the nature of information disclosed varies. In interviews conducted with 23 IRB chairs from 2004 to 2005, 61% of interviewees supported COI disclosures to subjects in all circumstances.<sup>21</sup> Of 120 respondents to a 2004 survey about their institution's policies, 48% noted disclosing financial ties to prospective subjects.<sup>20</sup> Since these studies were published, the roles of bias in clinical research and public scandals have brought attention and change to federal policy.<sup>22,23</sup> In the case, an IRB would likely have required some disclosure if Dr A has a "significant financial interest," as defined by federal policy, in Company K. For example, if Dr A received more than \$5000 in dinners and speaking fees over the past year, an IRB would have likely required disclosure to patient-subjects.

Yet, as noted, it's important to acknowledge uncertainty about whether and to what extent COI disclosure to participants achieves the 6 goals articulated above. Lay people often have limited understanding of the information disclosed, its intended meaning, or what it could mean for them, and they remain uncertain about which questions to ask.<sup>17,18,19</sup> In Weinfurt et al's study, several participants supposed that investigators with financial interests in research outcomes would conduct themselves more ethically and would do a better job.<sup>17</sup> It's also possible that disclosure might exacerbate investigators' bias,<sup>24</sup> particularly if investigators feel that disclosure constitutes sufficient warning to others and absolves them of responsibility to avoid bias.<sup>25</sup>

### Recommendations

Concerns about the efficacy of disclosures should not lead us to forego them. Transparency is ethically appropriate, and disclosure promotes transparency between investigators and research participants. However, further research on the actual influence of disclosures on all stakeholders' decisions is important, and we must acknowledge the limitations of disclosure in mitigating COIs. The AAMC-AAU report<sup>14</sup> and an Institute of Medicine report<sup>26</sup> both articulate standards for when investigators with

COIs should be able to conduct research, but whether AHCs commonly meet those standards remains unclear. Disclosures to participants are worthwhile, but greatly reducing or eliminating the conflicts to begin with is likely to be a much more effective strategy in reducing the risk of bias from an investigator's COIs.

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**Editor's Note**

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