

Opinion

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## **Serving Mammon: Conflicts of Interest in the Professions**

By Gregory K Pike, Deputy Director

"What's the worst that can happen to me?" he told a friend shortly before he left for the Penn hospital, in Philadelphia. "I die, and it's for the babies."

Tragically, Jesse Gelsinger's offhand remarks were prophetic. Soon after, he died while participating in a gene therapy trial at the University of Pennsylvania. He was just 18 years old, and the heartbreak for his family was heightened by the fact that his illness, ornithine decarboxylase deficiency, was already controlled by diet and medication. He was not seriously or terminally ill, unlike many patients in gene therapy trials.

The investigation that followed revealed a litany of failures of protocol, informed consent and disclosure. The director of the University's Institute for Human Gene Therapy was identified as having a financial conflict of interest by having financial arrangements with the company that funded work at the Institute. He and other researchers also owned patents on aspects of the procedure involved. They had interests in the success of the trials that had the potential for conflict with the interests they had in patient safety and the scientifically rigorous conduct of the trial. Those secondary pecuniary interests also had the potential to oppose and undermine their broader primary professional interests in the academic pursuit of knowledge.

Following Gelsinger's death the National Institutes of Health (NIH) sent out stern reminders to gene therapy investigators about the legal requirement to immediately inform the NIH of any serious adverse events. 691 reports came back, 652 of which had not been previously cited. Hence, a mere 6 percent were reported on time, and one wonders if they might ever have been reported without prompting by the NIH. Some of these cases involved patient deaths, raising the possibility that Gelsinger's death was not the first in a gene therapy study. Furthermore, there was the uncomfortable prospect that his death may have been averted if the NIH had timely knowledge of those other serious adverse events.

The extent to which conflicts of interest contributed to Gelsinger's death cannot be accurately known. However, his family did file a lawsuit alleging negligence and fraud, including the charge that the "defendants intentionally failed to disclose their conflicts of interest."<sup>1</sup> The suit was settled, but the terms remain undisclosed.

Referring to the circumstances surrounding Jesse's death, his father Paul Gelsinger was later to note,

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<sup>1</sup> Jesse A. Goldner, Dealing with Conflicts of Interest in Biomedical Research: IRB Oversight as the Next Best Solution to the Abolitionist Approach. *Journal of Law, Medicine & Ethics*, 28, 2000, 379-404.

“This is all about money, prestige. We forgot the basic point of it all: people.”<sup>2</sup>

Had Jesse been fully informed about all of these matters, it is possible that he may not have entered the study. Informed consent in this context is problematic. As bioethicist Arthur Caplan notes:

We know that informed consent doesn't work. The privatisation of science, combined with patients' ardent desire for a cure, conspire to prevent meaningful protections for participants in all kinds of studies. Trade secrets, financial conflicts of interest and overloaded review committees obstruct informed consent by keeping news about ongoing studies beyond the reach of patients and researchers alike.<sup>3</sup>

In a recent study of the views of potential participants in clinical research, the majority responded by saying that knowing about possible conflict of interest on the part of researchers or institutions was “extremely” or “very” important, and that individual conflicts of interest were more troubling than institutional ones.<sup>4</sup> The authors of the study conclude that the views of potential participants are at odds with current practice.

... it appears that the current practice of non-disclosure of worrisome conflicts of interest do not conform to the values and wishes of potential patient volunteers without whose participation no research can occur.<sup>5</sup>

In the recent debate in Australia about the use of human embryos in research, some of the most vocal proponents had financial interests in companies that were involved in embryonic stem (ES) cell research. If the legislators allowed the research and it proved successful, the proponents would stand to make considerable financial gain. Conversely, if the government prohibited the work they would lose financially.

Early in the public debate, some of these financial interests were not disclosed, so that when the public followed media reporting on the issue, they would naturally have assumed that scientific experts were giving an unbiased assessment of the potential therapeutic gains being claimed of ES cells. As it was, there were many others who voiced the opinion that ES cell therapeutic claims were well and truly hyped. The point is, the public debate probably had significant influence upon the final decisions of legislators, as did submissions made to governmental boards of inquiry. And a potential financial conflict of interest was something the public and decision makers would want to know about so that they could form a view of potential bias. The person with that potential conflict of interest can claim till they're blue in the face that the money had no

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<sup>2</sup> Peter Westmore, Bioethics: Gene therapy business: the tragic case of Jesse Gelsinger. *News Weekly*, 12 Aug 2000. Available online at [http://www.newsweekly.com.au/articles/2000aug12\\_bio.html](http://www.newsweekly.com.au/articles/2000aug12_bio.html)

<sup>3</sup> *Ibid.*

<sup>4</sup> S.Y.H. Kim *et al.*, Potential research participants' views regarding researcher and institutional financial conflicts of interest. *Journal of Medical Ethics*, 30:73-79, 2004.

<sup>5</sup> *Ibid.*

impact on their position, but that is beside the point. It is up to others to decide whether their advocacy was skewed.

A particular pressure experienced by advocates of ES cell therapies would exist in the possibility that potential funders of research may be less likely to support research programmes if a principal investigator spoke unfavourably or even neutrally about clinical applications coming from the research. Hying it up is seen as part of the game. Negative criticisms could easily result in a cold shoulder from a putative funding source.

Conflicts of interest can take many forms, but their basic nature is a conflict between a primary interest such as a physician's commitment to the health and welfare of a patient, or a researcher's interest in impartially pursuing accurate scientific information and interpretation, and secondary personal interests like financial gain, career advance or recognition.<sup>6</sup> While none of these personal interests are wrong in themselves – indeed they might be considered legitimate interests – it is the extent of their influence that counts, and this is related to their proximity to the primary interest, as well as to the virtue or otherwise of the person(s) involved.

Two different people presented with the same set of potential conflicts of interest might respond quite differently. One might be far more honorable than the other, and hence less likely to be influenced by personal gain. The other may be so deeply drawn by the prospect of financial gain for whatever reason, perhaps even their own financial hardship, that their judgment is more readily skewed and perspective distorted. Hidden or unconscious biases are hard to ascertain and yet they exert highly variable pressures upon an individual's judgment. Because of these sorts of influences, some level of conflict of interest seems inevitable.

The proximity of the secondary interest to the project about which the primary interest centers can also influence the potential for conflict. For example, a pharmaceutical company might provide \$1500 for each patient that a physician-researcher recruits into a trial.<sup>7</sup> Some of this money will support the trial and other costs, and some will end up with the physician-researcher. The level of distortion of the physician-researcher's judgment about eligibility for the trial that this money provides is likely to be less than the influence exerted by say the offer of royalties from sales of the drug being studied. The recruitment incentive is more closely related to the determination of patient eligibility than is the possibility of royalties, even though the financial gain from royalties could be substantial. The likelihood of reaping financial reward from royalties is more closely related to the successful outcome of the trial, and even though this depends to

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<sup>6</sup> A more problematic area involving potential conflicts of interest is the influence of ideological perspectives on primary interests. The reason this is problematic is not only because these interests are so varied, individual and hard to define, but also because they encroach upon belief and world-view. Extending concerns over conflicts of interest this far becomes unworkable as well as having the potential to threaten debate that ought to be based on the merits of the argument alone (for a more thorough analysis of this issue see Lynn A. Jansen & Daniel P. Sulmasy, *Bioethics, Conflicts of Interest, and the Limits of Transparency*, Hastings Center Report, Jul-Aug, 2003, 40-43). Nevertheless, in the drug policy debate for example, some vocal advocates for a permissive approach to drug policy have been prepared to significantly play down well-researched harmful effects of substances like cannabis, ecstasy, heroin and hallucinogens, because to do otherwise would jeopardise their commitment to their stated goals.

<sup>7</sup> A notable example in which this type of conflict of interest resulted in harm to a patient occurred in 1995 where a patient was entered into a clinical trial for a new drug despite not fitting the eligibility criteria. The doctor was being paid \$1650 by a pharmaceutical company for each new patient he recruited. The patient had to be removed from the study and hospitalised when he developed serious side effects to the drug because of a prior heart condition that was ignored by the physician. Kurt Eichenwald & Gina Kolata, *Drug Trials Hide Conflicts for Doctors*, *New York Times*, May 16, 1999, pg 1.

some extent upon recruitment, royalties are more likely to distort things like statistical analysis, interpretation of data and reporting of findings.

In light of this possibility, what do we know of the possible bias that conflicts of interest exert upon published studies? Examples can be found in several different fields. A case in point concerns the health effects of passive smoking. Reviews on this subject have been shown to be influenced by whether the authors received funding from the tobacco industry. Reviewers were more likely to conclude that passive smoking was not harmful to health if they were receiving industry funding,<sup>8</sup> suggesting that a conflict of interest may have swayed their judgement.

Similarly, studies funded by pharmaceutical companies into the efficacy of a drug that they are developing are generally more positive than studies conducted by researchers with no connection to the industry.<sup>9</sup> In a 1998 study on calcium channel antagonists for the treatment of cardiovascular disorders, the authors concluded:

Our results demonstrate a strong association between authors' published positions on the safety of calcium-channel antagonists and their financial relationships with pharmaceutical manufacturers.<sup>10</sup>

To put it another way, authors with financial ties to industry were far more supportive of the use of these controversial medications than were authors who had no financial ties, the majority of whom were critical. Furthermore, only about 3 percent of those who had ties to industry disclosed their connections.

The influence exerted by pharmaceutical companies spreads further than research and more directly into the realm of the doctor/patient relationship. This influence is exerted in the form of gifts to the medical profession for the purpose of influencing prescribing practices. Clearly, if physicians prescribe more, the company involved benefits more, and it is this influence that has the potential to become a conflict of interest for physicians whose primary interest is the health and well being of their patient.

Gift giving is a well-established practice and involves all manner of gifts ranging from trinkets like pens and note-pads to fully funded trips to conferences held at resort locations. In a biting editorial in the *British Medical Journal* (BMJ), the authors opened with the following sting:

Free pens and pizza lunches. Sponsored conferences and compromised medical education. Courtesy golf and unaffordable holidays. Thought leaders and ghost writers. These are the trappings of doctors and drug companies being entwined in

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<sup>8</sup> Deborah E. Barnes & Lisa A. Bero, Why Review Articles on the Health Effects of Passive Smoking Reach Different Conclusions. *Journal of the American Medical Association*, 279:1566-1570, 1998.

<sup>9</sup> Joel Lexchin *et al.*, Pharmaceutical industry sponsorship and research outcome and quality: systematic review. *British Medical Journal*, 326:1167-1170, 31 May 2003.

<sup>10</sup> Henry Thomas Stelfox *et al.*, Conflict of interest in the debate over calcium-channel antagonists. *New England Journal of Medicine*, 338(2):101-106, 8 Jan 1998.

an embrace of avarice and excess, an embrace that distorts medical information and patient care.<sup>11</sup>

The authors continue by noting:

Both doctors and drug companies know there is something unhealthy in this relationship, but seem unable to stop themselves.<sup>12</sup>

In a separate article in the same issue of *BMJ*, Moynihan identifies 16 different forms of entanglement, noting that from the earliest stages of medical training physicians have come to expect gifts in one form or another from the industry.<sup>13</sup> Like an accepted right of entitlement, gifts have become routine even though from the outside looking in, they have all the trappings of bribery.

Indeed, bribery is precisely the way Mansfield describes the practice, even though he acknowledges that there are “strategic reasons for continuing to call bribes “gifts”.”<sup>14</sup> Mansfield’s paper is a response to an article by Katz, Caplan and Merz,<sup>15</sup> in which they argue that even small gifts have the capacity to influence the receiver. Even though Goodman lauds Katz *et al.* on this point, he thinks they should “have thought twice about accepting a gift from industry for a paper about accepting gifts from industry.”<sup>16</sup>

If Katz *et al.* are correct, and small gifts have the ability to influence the behaviour of physicians, then what is the mechanism by which something so trivial, such as a pen or notepad, has this seemingly disproportionate power? The reason is that small gifts are really tokens that are a manifestation of a relationship, or more correctly in this case, of a friendship forged between physician and company representative. Gift-giving is associated with a powerful sense of obligation; what might be called the reciprocity rule, and this is why the size of the gift is disproportionate to the obligation felt.

Physicians can carry a sense of indebtedness without even being aware of it, and even deny that it exists at all. Indeed, those who most often deny the power of small gifts to influence their prescribing behaviour are the ones who receive the most gifts.<sup>17</sup> And the association between gifts and influencing prescribing behaviour is now well established, so that these doctors are also likely to be the ones most influenced.<sup>18</sup>

Interestingly, the gift-giving patterns of the pharmaceutical industry are closely-guarded secrets, and one wonders why. Could it be because their disclosure would reveal a

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<sup>11</sup> Kamran Abbasi & Richard Smith, No more free lunches: Patients will benefit from doctors and drug companies disentangling. *British Medical Journal*, 326:1155-1156, 31 May 2003.

<sup>12</sup> *Ibid.*

<sup>13</sup> Ray Moynihan, Who pays for the Pizza? Redefining the relationships between doctors and drug companies. 1: Entanglement. *British Medical Journal* 326:1189-1192, 31 May 2003.

<sup>14</sup> Peter R. Mansfield, Bribes for Doctors: A Gift for Bioethicists? *American Journal of Bioethics*, 3(3):47-48, 2003.

<sup>15</sup> Dana Katz, Arthur L. Caplan, & Jon F. Merz. All Gifts Large and Small: Toward an Understanding of the Ethics of Pharmaceutical Industry Gift-Giving. *American Journal of Bioethics*, 3(3):39-46, 2003.

<sup>16</sup> Bob Goodman, All Rationalizations Large and Small. *American Journal of Bioethics*, 3(3):57-58, 2003.

<sup>17</sup> Hodges, B., Interactions with the pharmaceutical industry: Experiences and attitudes of psychiatry residents, interns and clerks. *Canadian Medical Association Journal* 153: 553-59, 1995.

<sup>18</sup> Katz *et al.*, *Op. Cit.* 2003.

cleverly devised strategy pin-pointed towards yielding the best outcome for company profits? Could it also be that to do this, drug companies gather information about individual doctor's prescribing behaviour to best target and dose their gift-giving, and this looks like they know exactly what they are doing and more like bribery?<sup>19,20</sup>

Whatever anyone thinks about these drug industry strategies, it is important to be aware that they are only one arrow in the quiver. For example, other methods that create conflicts of interest of a different sort involve direct to consumer (DTC) marketing. This technique involves seeking to influence the physician's prescribing practice indirectly via the patient. Here the patient receives the gift – in the form of coupons for discounted or free product – and applies pressure to the physician to prescribe that product. This type of influence is not a conflict between the physician's primary and personal interests, but between the physician's primary interest to provide the best treatment for a patient, and a competing interest to assist the patient who may benefit financially. Of course a minor and competing personal interest may be to silence a persistent patient who "knows best" about the prescription they should receive because of the advertising they have been presented with.

The next question then, concerns what should be done about conflicts of interest. Is the most obvious strategy, disclosure, enough?

If a physician or the drug companies were to disclose to patients the business of gift-giving from the pharmaceutical industry would that make any difference to their prescribing patterns? Possibly, although the subtleties of the influence of gifts seem lost on many physicians themselves, and therefore it is unlikely that their prescribing behaviour would become more objective simply by announcing to their patients that drug companies give them a variety of small and large gifts. This is why there have been many calls for a complete disentanglement of gifts from doctors.<sup>21</sup>

In other contexts, however, disclosure might resolve conflicts of interest. For example, when authors disclose their financial ties to companies, readers may be able to form their own opinion about possible bias. But in other areas, such as research directly funded by industry, disclosure is insufficient and something more refined and perhaps regulated is required that will take much careful deliberation to work through. Too much is at stake simply to rely on disclosure as the remedy for making research entirely trustworthy. Moreover, as Virginia Sharpe notes:

... statements of potentially biasing affiliations can be a stratagem to shift responsibility from the producers of risk or known harms to the individual exposed to them (who may not understand what she is being told).<sup>22</sup>

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<sup>19</sup> Howard Brody, Pens and Other Pharmaceutical Industry Gifts. *American Journal of Bioethics*, 3(3):58-60, 2003.

<sup>20</sup> Rosamond Rhodes, The Invisible Influence of Industry Inducements. *American Journal of Bioethics*, 3(3):65-67, 2003.

<sup>21</sup> Kamran Abbasi & Richard Smith, *Op Cit.*, 2003.

<sup>22</sup> Virginia A. Sharpe, Reply to: *Disclosure – Is it Enough?* by Larry Scott, *Hastings Center Report*, 33(3): 4-5, 2003.

But what of conflicts of interest in a profession like bioethics, where increasingly bioethicists are acting as paid consultants in a variety of different settings? Should those financial arrangements be disclosed? Is there something about bioethics that suggests disclosure is inadequate and the mere presence of a potential conflict of interest cannot be tolerated?

Recently, the *Hastings Center Report* tackled this matter with a series of articles that revealed some deep divisions in a still young discipline. In an opening article in the May-June 2002 issue of the *Hastings Center Report*, Brody and others argued in favour of bioethicists acting as paid consultants and that there were even circumstances in which disclosure was inappropriate.<sup>23</sup> In their own disclosure at the end of the article they stated that they had “performed consultations of the type described in this article,”<sup>24</sup> but declined to say with whom they had financial ties and for how much money. Most of the article describes operational matters in paid consultancies.

In a critique of the lead article, Stuart Youngner and Robert Arnold were clearly unimpressed, even though they agreed in principle with the adequacy of disclosure. Nevertheless, they describe the publication of this article in the following way.

A unique and troubling moment in the maturation of bioethics. The flagship scholarly journal of bioethics has published a “how to” manual for a new guild interested in promoting what it already does.<sup>25</sup>

As part of the same debate, Neil Boyce, a journalist, goes further by questioning the role of the bioethicist and whether such a role should even allow for potential conflicts of interest like paid consultancies. Most of the people he asked

... expressed dismay at the idea that someone described as an academic bioethicist and quoted in the national media might benefit in some way from corporate money.<sup>26</sup>

And,

The disapproval that they have expressed to me implies that they see bioethicists as having a public service role akin to that of a journalist, a government official, or a judge. For professions like these, disclosure of conflicts isn’t usually enough – their mere existence threatens the public’s trust.<sup>27</sup>

The difficulty with this position is that it not only places bioethicists in a role somewhat like a secular priest – one that many have been at pains to avoid – but it also means

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<sup>23</sup> Baruch Brody, Bioethics Consultation in the Private Sector. *Hastings Center Report*, 32(3):14-20, 2002.

<sup>24</sup> *Ibid.*

<sup>25</sup> Stuart J. Youngner & Robert Arnold, Who will watch the watchers? *Hastings Center Report*, 32(3):21-22, 2002.

<sup>26</sup> Neil Boyce, A View from the Fourth Estate. *Hastings Center Report*, 32(3):16-17, 2002.

<sup>27</sup> *Ibid.*

that bioethicists are cut off from a source of income that might be the difference between survival and closing up shop. For the time being at least, transparency by way of full disclosure will remain the predominant means for bioethicists to manage potential conflicts of interest.

In addition, adherence to an ethic that upholds integrity, honesty and the relegation of self-interest to its appropriate place will do much to avoid conflicts of interest and importantly even the appearance of a possible conflict of interest.