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FACTS AND FRICTIONS: CONFLICTS OF INTEREST IN MEDICAL RESEARCH

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Overview

I'm going to give you a bird's eye view, as an editor-in-chief, of why conflict of interest in medical research is such a vital problem today in medicine. By the time I am finished, I hope that I will convince you that we physicians and medical scientists need to make sure we take control of our profession to protect our patients in a way that only we can do.

The first definition of "conflict of interest" that I could find goes back to 1850 in *Webster's Dictionary*: "To conflict between the private interests and the official responsibility of a person in a position of trust." That sounds familiar to all of us in medicine, because that's who we are. Why do authors and reviewers have conflicts of interests? Career advancement, peer recognition, competing research interests, competition for research grants, intellectual biases and passions, and financial conflicts that we sometimes let get in the way. Editors have conflicts of interest because we want to promote our journal and improve our "impact factor"—a measure of the average number of citations to articles published in scientific journals. The impact factor is often used to gauge the relative importance of a journal within its field. I would love to do away with this. It is the most manipulative thing in the world because journal editors have to live by it, and departments use the impact factor as a mechanism for promotion. Editors also want to increase subscriptions and increase the financial profitability of their journals; sometimes, they have a conflict of interest because they're trying to eliminate or decrease stress, hostility, or harassment. In fact, I invite anyone who *doesn't* think a journal editor deals with stress, hostility, or harassment to spend a day with me.

The Financial Conflict of Interest

A financial conflict of interest includes any paid affiliation or financial involvement with any entity that has an interest in the subject of or materials in a study. It is pervasive, it is increasing, and it is undergoing intense scrutiny. If you doubt that, you haven't been reading the papers.

A financial conflict of interest usually involves remuneration in some form — either material or financial. Let's say that someone takes you out to a fancy restaurant or invites you and your spouse to a nice resort. They talk to you about how great their product is and then casually ask, "Oh, coincidentally, will you be in our speaker's bureau?" This involves both a material and financial interest; it has to do with affiliations and consultant fees. It means you would be on a speaker's bureau where you are being paid by and working for the *marketing* part of the for-profit company, not the scientific part.

Let me be clear about the term "consultant fees": There is nothing wrong with a physician or clinical scientist consulting with a for-profit company. Who better to advise these companies on what medications and what devices are needed? There should be a reasonable fee for your time and your energy, and that's legitimate. The fees I'm talking about are those so-called "consultant fees" where you show up and someone hands you a completed study that's already been researched and written, and all they want to do is put your name as first author. That's not exactly a consultant's fee. Yet that's the kind of thing that's going on.

Science and profit: are they partners or enemies? This question has drawn increased scrutiny and skepticism from the public. There are several issues at play, including the privatization of biomedical research, the financial self-interests of clinical investigators, and an increased awareness in the tension in biomedicine throughout the world. There's heavy literature on the subject, with the focus mostly on industry and questionable relationships.

Ethical Considerations: The Issues of Influence

I did a PubMed search on articles about conflict of interest from 1974 to 2009. There's essentially nothing going on until the late '80s, and then it starts taking off, with more than 500 articles annually in PubMed on the topic. So what happened? Well, pharmaceutical and for-profit companies have two divisions: the scientific division, with some of the greatest scientists and biostatisticians in the world, and the marketing department. The marketing people are trained to sell devices and drugs. The CEOs of the big companies realized that it was costing an incredible amount to develop a new drug — the figure I was given was $800 million dollars. That's a lot of money. If they could take something that has *already* been approved by the FDA and find new uses or sell it to people who don't really need it, they could generate revenue without the cost of developing something new.

Look at Vioxx, for example. Vioxx was a very good drug for arthritis and pain relief, appropriate for maybe about a million people. What happened is that Vioxx was being heavily promoted in marketing campaigns featuring Olympic champion Dorothy Hamill *after* studies showed that Vioxx significantly increased the risk of myocardial infarction. Those folks who relied on the drug, who were in constant pain, were willing to take that risk because

Vioxx was the only medication that made their lives anything but miserable. Yet because of clever marketing, it was being promoted and sold to probably 20 times the number of people who actually needed it, where other less-expensive and certainly less-toxic drugs could have been used. So the problem is that companies have shifted the money over to the marketing side and out of the research side. At every national meeting I attend, scientists who work for these companies tell me that they are frustrated because the resources are no longer the same — money once given to them for development is now going into marketing.

What influences this conflict between science and profit? I have a list of the top-spending sectors that are lobbying Congress and federal agencies. At the top of the list are pharmaceutical and health care products. In 2008, $4 billion was spent on direct-to-consumer marketing of drugs and other health care products. And here's the result: you're a physician and you've got 6 to 10 minutes with a patient on average. A patient comes in with a coupon for a drug. You could spend six minutes telling him why you really don't think that's the best drug for him, or you can just write the prescription. Of course, the next time they fill the prescription they will have paid probably 10 times what they would have paid for a generic that may have worked just as well.

When it comes to funding in biomedical research, here lies another problem. If you look at the amount of money being spent on funding biomedical research, the big money is from medical device firms, biotechnology, and pharmaceutical funds. These make up about 60% of spending. If you look only at clinical research, not basic science, it makes up over 80% of all money that's spent on research. Is that wrong? No. Pharmaceutical and biotech companies *should* spend that much money and then make a decent profit for doing it. The problem is what happens during the research phase and sales of these new discoveries.

Why does all this matter? Well, financial relationships can often affect what authors publish — it can affect when, how, and, in some cases, even if research is published. I went to a meeting of the International Committee of Medical Journal Editors (ICMJE) 6 years ago. We had no legal jurisdiction; all we had were pretty decent journals — *JAMA, New England Journal of Medicine (NEJM), BMJ, Annals of Internal Medicine* — and all we could do was decide what gets published in our journals and what doesn't. So I brought an issue to the table that bothered me, because I wanted to know if it troubled anyone else. I asked, "Am I the only one who receives a clinical trial, and everything looks fine on it except that I don't know how many trials before it didn't look so good?" Because even though there was a law in the United States that said all trials must be registered, nobody seemed to pay attention to it. Can you believe that 12 editors agreed on something? We not only agreed this was a problem, but we put together an editorial that was published in all 12 journals simultaneously, which said, "If you want to publish a clinical trial in our journal, you have to register it the day that you enroll the first patient."

I persuaded the Institute of Medicine to host a meeting with the pharmaceutical companies, which didn't like this policy at all. Three of us met with them: myself, Jeff Drazen, editor-in-chief of the *New England Journal of Medicine*, and Harold Sox, editor of *Annals of Internal Medicine*. Their excuse for not agreeing with our policy was, "Well you know, we'll be giving away our secrets." So we went back and forth and back and forth. And a representative of the FDA asked me why I should care. I said, "Excuse me, who are you supposed to represent? I care because if people are going to use my journal and my integrity to advertise their product by publishing their study in my journal, I first want to make sure that under these circumstances, in this population, this research looks good." However, there were three other studies in a different population under different circumstances where the drug or device didn't work. And I want to be able to put that in the discussion.

The bottom line is that it's the law, but we gave them a year to catch up. One week before the end of the time they had to enroll their studies, I received a clinical trial that was very nicely done. I called the author and said, "You didn't register this." And he said, "You're kidding." I told him I wasn't. I didn't know it but Jeff Drazen at the *NEJM* also received a nonregistered trial, although a different one, and we both turned them down. Within 1 week, 4,000 clinical trials were registered. The rest is history: you don't register it, we don't publish it. As editors we had no legal jurisdiction. However, we did control when we published and believed that research should be reported accurately, and we all stuck together. That's the power that you have if you truly believe something is wrong and you want to fix it.

When I came to *JAMA* in 2000, I told the publisher that I knew we had to publish ads. I would personally love to do away with them, but legally and financially I can't keep them out. The one thing I can do is to make sure that what we publish is legitimate. I will not publish advertorials, and I will never allow the for-profit company ads to go only in one specific issue. The advertiser is not allowed to pick the issue. Now, if you buy five or six ad runs, one of the issues may by coincidence include something about a particular product that is related to something that company makes. But this is purely by accident; neither the advertisers nor anyone in the AMA know what we are publishing until it's in print.

I was at *JAMA* about 3 or 4 months, and I got a call from our ad people. They said, "Dr. DeAngelis, we just got an order for a wonderful four-page centerfold, and if you only want to read the science, you can rip it out, but they know it will come before or after the scientific articles." However, they only wanted it in this one issue, and it was a company that didn't advertise very much. So I looked at what was slated for that issue, and sure enough it included something about one of the few products made by that company. I called back our ad folks and said, "I'm sorry. They can have any issue but that one." I got a call back maybe 15 minutes later saying, "Dr. DeAngelis, that's the only issue they want. This is a *big* order." So I thought about it, and I said, "Okay, we'll put it in." And they said, "Really?" And I said, "Yeah, put it in." And then I moved the article ahead 2 weeks. That action made the point, although it did so at the chagrin of the advertiser.

Now, what is the prevalence of these financial interests? It goes way back — I can find things in the literature beginning at about the late 1980s. When I put them all together, at least one in four investigators has industry affiliations. I'm not talking about legitimate ones like getting research grants from the company. I'm talking about other kinds of affiliations — speakers bureaus, that sort of thing. There's a very high association between industry sponsorship and the research findings. If a study comes through that was sponsored by a company that has an interest in the results, it is four- to eight-times more likely to be positive than if it's not sponsored by that company.

Let me give you a couple of examples of studies that involve financial interests:

- From the *NEJM*: The authors who supported calcium channel blockers were more likely than neutral or critical authors to have financial relationships with manufacturers who made CCBs (96% versus 60% and 37%, respectively).
- From *JAMA*: Industry sponsored studies of cancer drugs reached unfavorable conclusions much less often than studies with nonprofit funding (5% versus 38% unfavorable conclusion).

- From *JAMA*: This study looked at 192 authors of 44 practice guidelines — which most physicians use to determine how to treat patients — between 1991 and 1999. Of those 192 authors, 59% had relationships with companies whose drugs were in the guideline, 7% believed the relationship influenced their personal recommendation, and 19% believed that their colleagues' relationships with the companies influenced their recommendations. "Not me, him."

Delay of Publication

There is a 1995 study of more than 2,000 life sciences faculty in the top 50 NIH-funded universities. Almost 20% of the respondents delayed publication of articles for more than 6 months to serve proprietary needs — to allow for patent application or negotiation, to protect the scientific lead, to slow dissemination of undesired results, or to resolve intellectual property ownership disputes. Suppression of results is a legal action to suppress or delay publication. Remember the famous Olivieri case that was published in the *New England Journal of Medicine*? She was researching the effectiveness of deferiprone, a potential orally administered chelating agent, and found that deferiprone could actually worsen hepatic fibrosis. The sponsoring company was able to delay publication for 3 years because its contract with Olivieri prohibited her from disclosing the results without the company's consent. So they held it up in court 3 years until it was finally published, although by then the patent was almost up anyway. Another study in *JAMA*, this one by Dong et al. from the UCSF School of Medicine, evaluated the effectiveness of Synthroid in treating hypothyroidism and found it to be equivalent to generic thyroxin rather than more effective. The company delayed publication for 4 years.

In my first year at *JAMA*, there was a study by Dr. Khan from UCSF, and the company was allowed to delay it in court because as the contract was written, the company controlled how, when, where, and if the study got published. The university scientists doing the study had no control over that. Along comes Dr. Khan about 5 years later. He calls me one day and he says, "Dr. DeAngelis, you know there's this famous HIV immunogene, a vaccine that we've been studying? It doesn't work. I don't have 15% of the findings because this is a multiple-site study and the company won't give me 15% of the data. But I know it doesn't work. We have people who received this vaccine who should be receiving drugs that prolong their life, and they can't because they are in this study, receiving this vaccine, and they think it will protect them." He asked me if I would look at this study, and of course I said I would. I had four statisticians look at it, and they said there was no way that it worked, even without the 15%. So I decided to publish it with an editorial that explained why we were publishing a study that didn't have the power to scientifically prove ineffectiveness. Then I received a call one day from a man who said he was Jones of "Ratzafratza" and Jones (or something like that). I said, "Excuse me, sir. Are you a lawyer?" He was. So I told him I didn't speak legalese and gave him the number of our lawyer. And he says, "No, lady, I'm talking about you. I'm going to sue you." So I thought about it for a minute, and I then developed my favorite "Japanese" word, "sosueme." They didn't. Instead, they tried to sue UCSF for $8 million dollars, and they lost. They lost because these were the same lawyers who did the Dr. Dong contract 5 years earlier. This time, the full control over where it was published, when it was published, and how it was published was in the hands of the UCSF faculty and not the drug company.

Hiding Bad News

Then there is the situation of deliberate lying, which also happened during my first year at *JAMA*. This one involved the drug Celebrex, which was supposedly associated with lower incidence of gastric ulcers and ulcer complications. This was planned as a 12-month study, but the authors said the company only had 6 months of data. I made the editor who was handling this article ask them three times, "You don't have 12 months? It looks great after 6 months, but you don't have the 12 full months?" And they replied, "No, we don't have it." I even got it in writing. Then we found out that they lied. As soon as it was published, I had phone calls from two different people who said they had 12 months of data and it doesn't work. It looks protective for gastric bleeding for the first 6 months, and then it actually caused more or at least the same bleeding after another 6 months. We made the authors write a letter of apology, and we published that letter and the corrected data.

Potential FDA Approval

How many of you have ever heard of muraglitazar? This was supposedly the billion dollar drug to control blood glucose and triglycerides. It's well known that those with adult onset diabetes are usually on a glucose-lowering medication and a lipid-lowering medication. This was a drug that supposedly combined both, so you could take one pill in the morning to lower both your triglycerides and your blood sugar. I read about it in *The Wall Street Journal*, and I thought, "I'd like to find out who's doing this because I'd like to publish this study. It looks like a great drug." On September 8, 2005, the FDA Advisory Committee voted 8-1 to approve this drug. Then I got a call from somebody who said, "Cathy, this drug is dangerous."

I said, "What do you mean it's dangerous? The FDA just voted to approve it."

He replied, "There isn't one cardiologist on that committee — out of nine members, not one cardiologist."

"Well, how can that be?" I asked him. "Why aren't *you* on it? You're on the FDA list of potential committee members."

He said he couldn't because of his involvement with other similar drugs. But then he said, "I have the data and I've analyzed it. It's a dangerous drug. Will you look at the study?"

So once again, I had our biostatisticians look at this study, and the problem was that the company conducted the statistical analysis in a way that made it look like it was okay to kind of bury the adverse cardiovascular events. But if it had been done correctly, you'd see it was dangerous. Again, four reviewers and every one of them said it was a dangerous drug. So I published it. In early October, I read that a press conference was planned to announce the probable FDA approval letter, and the pharmaceutical company needed some clarification from the FDA saying, "We want you to follow the first 10,000 patients." But the FDA has no power to enforce that, so the drug companies never do it. I published the article online in October, and immediately I got calls from the press asking why I posted it early online. I replied that I knew the company was due to have a press conference about the FDA's announcement, and I just wanted to make sure everybody knew.

And they asked, "Who do you think is right?"

So I responded, "I really don't know. But I want everybody to see that there's another way to analyze this data."

They also asked what I thought the FDA would do, and I told them that they would do the right thing. What I didn't tell them was that I learned that the CEO of this company had contributed over $2 million to a very important politician's coffers. The next month, the company withdrew its request for FDA approval. They

said they had better drugs that were coming forth. I haven't seen them yet, but at least this drug never made it to the market.

Competing Interests

In 2009, we published a special communication called "Professional Medical Associations and Their Relationships with Industry," in which the authors identified and analyzed conflicts of interest that may affect the activities, leadership, and members of professional medical associations, and they formulated guidelines to prevent the appearance or reality of undue industry influence. I don't know how we ever got into this business, but so-called "continuing medical education" is almost completely controlled by the drug companies. And what frequently happens is that there is a presentation by an expert who is actually using slides prepared by the drug company, and they are talking about a drug that has been approved for a specific use by the FDA. Somebody in the audience, who is a plant, asks, "Have you ever tried using this drug for something that's not approved by the FDA?" And the presenter says, "You know, now that you asked, yes." And then a conversation ensues. So now you're teaching people how to use this drug for something that the FDA didn't approve.

Another interesting case was the marketing of the HPV vaccine. This occurred when politicians received funding to promote the use of the HPV vaccine, which may be a very fine vaccine. However, it has never been proven to decrease the likelihood of cancer. It does decrease the likelihood of getting cervical infection or disease, which in some cases can lead to cancer. But in many cases, the infection resolves spontaneously. If people want to use this vaccine, that's fine, especially if there are more than one or two partners. But when a politician makes it a law for sixth-grade girls to receive this in school, you start wondering. Now there are two cancers that have decreased over the last generation. One is lung cancer because people have stopped smoking. The second is cervical cancer. Why? Pap smears. People have already told me that they no longer need to have a pap smear because they think they're protected by the HPV vaccine. It's a misuse of political clout to promote a medical vaccine that may or may not be effective against cancer.

Setting the Record Straight

There was a commentary sent to us by Dr. Steven Nissen, the chairman of Cardiovascular Medicine at Cleveland Clinic. He's a controversial figure because some people think his scrutiny of drug companies is too far out there. All I know is that I checked out all the facts in his article, which challenged the findings reported by a particular drug company. After I read it, I wrote a three-page editorial with my executive deputy editor. The basic facts in this editorial were taken from a 250-page, 2-year investigation by the Senate committee of how the company manipulated the statistical analysis of this study to make it look like it was working.

This is why I'm trying to get all the ICMJE and other journals to insist on an independent statistical analysis by a faculty member before research is published. Right now *JAMA* is the only journal that requires this, and I know the drug companies do everything in their power, especially if it's a manipulated clinical trial, to avoid manuscripts being sent to us, because I will insist that an academic biostatistician look at it. Not because I think the academic biostatistician is more honest or smarter — but if you read this, you will see how the biostatisticians who worked for this company said that the research was accurate. Yet Dr. Nissen reviewed the research and found a high rate of adverse events. So the company basically told him, "Keep quiet, this is how we're going to handle it." Now, if the research is reviewed by an academic biostatistician, they can determine if the data is right or wrong. I have called four deans in my life when there was a question about the integrity of the data. All four times the deans responded that we were right. In one case we even retracted a paper. Whether or not it is warranted, the total result of all these cases arouses public concerns and threatens the viability of biomedical research.

The Role of Disclosure

Disclosure isn't perfect, but it's the best thing we have for now. We insist on disclosure in complete detail during the course of the study, up to the time of publication, and past the future considerations. If you have a patent pending, we want to know about it. If ever in doubt, disclose. Let the editor decide whether or not to publish it. One of the things that we're going to do at an upcoming ICMJE meeting is develop one disclosure form that is not only financial but ideological as well. We had a situation in which someone was bashing a paper we had published that addressed the use of antidepressants in patients after stroke. It is well known that depression is highly prevalent after a stroke, and a person left untreated is four times as likely to die within several years. The person attacking the paper did not disclose that he was a scientologist, because people would have realized that scientologists do not condone the use of medications for any reason. The new disclosure form will be standardized with all kinds of information, and every author can keep it updated on their desktop and forward to any journal as needed.

Conclusion

Conflicts of interest in medical research are a fact of life. Researchers, authors, editors, and readers must agree on a disclosure policy and ensure transparent reporting, because managing conflicts of interest appropriately is essential to ensure the public's safety and trust. The goal is to have those in the medical profession get together with the pharmaceutical and device companies and do this right, so that the outcome is better patient care. After all, that's what we're all about.