

GUIDING PRINCIPLES: WHERE ARE WE HEADED?

Moderator

NINA TOTENBERG

Legal Affairs Correspondent,
National Public Radio,
Washington, DC

Panelists

DARRELL G. KIRCH, MD

President and CEO,
Association of American Medical Colleges,
Washington, DC

PAUL A. LA VIOLETTE, MBA

Chief Operating Officer, Boston Scientific
Corporation, Natick, MA
Member, Board of Directors, and Chairman,
Special Committee on Codes of Ethics,
AdvaMed

NORKA RUIZ BRAVO, PhD

Deputy Director for Extramural Research,
National Institutes of Health,
Bethesda, MD

Panel discussion

Guiding principles: Where are we headed?

■ NIH ETHICS RULES: UNINTENDED CONSEQUENCES?

Ms. Totenberg: Dr. Ruiz Bravo, the National Institutes of Health (NIH) was under considerable pressure from Congress because of alleged conflicts of interest. The head of NIH then handed down a new edict, followed by a hue and cry from NIH employees and a perceived threat of a massive exodus of scientists. The head of NIH then eased the rules. I am unclear about the changes from the first edict and how they differ from the situation as it now stands. What is permitted now that wasn't permitted under the initial edict?

Dr. Ruiz Bravo: Actually, the rules were both handed down and subsequently eased by the Office of Government Ethics and the Department of Health and Human Services. One rule that NIH staff disliked was the absolute prohibition against consulting for "substantially affected organizations" [generally, pharmaceutical, biotechnology, and device companies]. This prohibition is still in place, but there is an NIH ethics advisory committee that looks at specific instances in which these activities may be performed, to ensure that they are done in a transparent way and according to the law. An NIH intramural scientist who is available to one company or one specialty has to be available to everybody. Consulting per se is no longer allowed.

Ms. Totenberg: So if MiserTech Pharmaceuticals from the fictitious case study in my prologue wanted to hire an NIH expert on cystic fibrosis to review some of its materials, under the auspices of teaching and writing, could it do so under the NIH rules and pay him \$10,000?

Dr. Ruiz Bravo: No, it could not. However, an intra-

Mr. LaViolette reported that he has no financial interests or relationships that pose a potential conflict of interest with this article apart from his employment with Boston Scientific Corp., from which he receives a salary and in which he holds ownership interest. All other participants reported that they have no financial interests, relationships, or affiliations that pose a potential conflict of interest with this article.

mural investigator may be able to collaborate in an official capacity (no compensation) with MiserTech. If it were in a public forum, on the other hand, then an NIH intramural investigator would be able to address specific issues that related to MiserTech.

Ms. Totenberg: What quelled the revolution among the NIH staff?

Dr. Ruiz Bravo: We have always had a prohibition against consulting with substantially affected organizations, but some NIH staff didn't know the rules. Having more exceptions and better education has helped, and over time staff have become more used to the rules.

Ms. Totenberg: The prohibition against stock holdings in those substantially affected organizations was new, wasn't it?

Dr. Ruiz Bravo: Yes, the divestiture rule is new.

Ms. Totenberg: How much divestiture had to take place, and how many scientists have you lost at NIH?

Dr. Ruiz Bravo: The overwhelming majority of NIH employees did not own stock in substantially affected organizations, and the divestiture rule was significantly changed from the interim final to the final rule: senior employees are the only ones subject to an absolute de minimis. So there has not been much divestiture. We have lost a few employees, although I don't have a number. Of those who have left, some may have left because of the ethics rules and some for other reasons. We have always had some turnover, but we have also been able to recruit some very good people. So I don't think it is necessarily the predicted end of NIH's ability to recruit good people.

Ms. Totenberg: One more impolitic question for you: What does the top scientist at NIH earn?

Dr. Ruiz Bravo: That information is publicly available. I think it's between \$200,000 and \$250,000 a year.

Comment from audience: This is Philip Pizzo from Stanford University. The NIH is the engine that has driven this nation's entire biomedical research efforts. I was part of the NIH community for 23 years as an intramural scientist; during my tenure there were initially quite strict rules about what one could do in terms of consulting or interactions with industry, but consulting was allowed. Then, in 1995, the NIH director at the time, Harold Varmus, decided not to accept guidelines that had come down from the Office of Government Ethics, arguing that the ethics rules should be liberalized in order to attract the best scientists to NIH. While these actions were well-intentioned, at that point the NIH was able to "freewheel it" somewhat, and that's when equity ownership came in, that's when the ability to consult largely began. This did have a series of unintended consequences because there were a number of people who did not play by the rules.

That helps to explain the impetus for the new NIH ethics rules, especially for the controversial "first edict," as Ms. Totenberg put it. I was on the oversight committee that NIH director Elias Zerhouni put together to develop the current rules. We did not advise him to go to the extreme that he did, but Congress got involved and said, "This is out of hand; do something about it." It was that external pressure that likely tipped his hand.

Similarly, if Congress begins to look at conflict-of-interest issues more broadly and decides it wants to extend the intramural NIH rules to everyone who receives an NIH grant, we'll be in a whole new world. At Stanford, all of our faculty are on "soft" money: if they lose their grants or their clinical revenue goes down, so does their compensation. We may be endowed as a university, but as a medical school, we have our own financial bottom line. So we don't have a lot of resources to be able to provide for research activities. If the NIH were to adopt a policy that extended the rules for their intramural scientists to the extramural community, it would have tremendous implications. That's been one of my fears from the beginning, and one of the reasons why Stanford is trying to self-police its activities.

Dr. Ruiz Bravo: We have been asked why NIH's intramural rules don't apply to extramural scientists. As federal employees, we probably should be held to a higher standard. We had this discussion in many quarters. It's incumbent upon the biomedical research

community to come up with its own rules. The principles by which NIH has come up with its rules are good ones, and perhaps they ought to be considered seriously by the biomedical research community in developing its own rules.

Question from audience: Dr. Ruiz Bravo, there is a dramatic difference in the way NIH is treating its intramural versus extramural scientists. Extramurally, NIH is promoting translation, which in some cases means giving money to university laboratories to set up small-molecule and animal testing. These extramural investigators are trying to discover drugs; they want to become companies right inside the university. These are the people who will develop new products, and NIH is promoting that. Yet inside NIH you are saying that those kinds of people are not wanted. I wonder how the quality of the people who have left NIH compares with the quality of those who have remained. Have you peeled out some of your potential inventors?

Dr. Ruiz Bravo: I want to dispel that notion that NIH no longer wants to have innovation and interactions with industry. We've simply set grounds for how interactions with industry are going to happen. But we do have these interactions and we certainly encourage them. The intramural program would

take a dim view of the notion that our employees who have stayed with us are not innovative and not among the best in the country, let alone the world. As I said during my presentation, public-private partnerships are very much a part of our future at NIH. The question is how to do it in a way that maintains scientific integrity and maintains our credibility with the public while also furthering the biomedical research enterprise.

Question from audience: Dr. Ruiz Bravo just said that we have to maintain scientific integrity. The corollary is that we maintain scientific integrity by banning consulting. There's a lot of talk about trust, but don't we also want results? The ban on consulting is not promoting results. It may be that a different standard is needed for government agencies like the NIH, but I worry that it's going to spill over to universities and that research progress will suffer as a result.

Dr. Ruiz Bravo: What evidence do you have that NIH research has suffered as a result of stricter ethics rules?

Same questioner from audience: I know companies that had to shut down scientific advisory boards

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because they had NIH investigators who were trashed by the *Los Angeles Times*. I believe that's the real reason the NIH rules were put in place.

Dr. Ruiz Bravo: You have a point of view, and I respect that. But there are other points of view as well.

■ SHOULD INVENTORS EVER SERVE AS INVESTIGATORS?

Ms. Totenberg: I want to ask about the relationship between doctors and medical device companies. If a company has a new device, obviously the company has to train doctors how to use it, and a personal relationship develops that doesn't necessarily exist for pharmaceuticals. Mr. LaViolette, if I invent a new implant for back fusion surgery and I have a protocol to test it, does the AdvaMed code of ethics allow me to also serve as one of the investigators in the clinical trial?

Mr. LaViolette: The code doesn't address that yet, and it's a legitimate question. If we allowed an inventor—someone who is likely to receive royalties or who has some financial interest—to participate in a way that was not part of the exploratory research but rather part of the pivotal research (performing the procedures, looking at data, etc.), I think that would taint the research and would be a bad idea. I think that most in industry, certainly in big industry, would agree that that type of scenario should be fully prohibited. However, if I were in the venture capital world and thinking about starting a company, and if the physician who invented the technology were world-renowned and heavily influential, I would probably fight to have that person involved all along the way. That's the rub: there's some distance between doing things for the right principle and doing things for the marketplace, and we still have not fully bridged that gap.

Ms. Totenberg: By the way, in the AdvaMed code there is a good deal of talk about modest gifts. What's modest? At National Public Radio, we're not allowed to accept anything worth more than \$20.

Mr. LaViolette: Modest to me is something that you get and then immediately give to your kids because you don't care about it. I guess that's in the \$20-or-less range.

■ WHO'S SETTING ETHICS STANDARDS, AND WHO'S ENFORCING THEM?

Ms. Totenberg: Dr. Kirch, I want to ask you about the

emerging ethics at academic medical centers. We've now seen Stanford and Yale University ban all gifts, including drug samples and lunches for residents. Those institutions, as I noted earlier, have pretty big endowments, and I would imagine that the heat is now on Harvard Medical School. When Harvard goes, and a couple of other major institutions follow, will those institutions set the standard and change the culture? Or will we end up with a bifurcated system where the big fancy institutions have one set of ethics and everybody else has a different set?

Dr. Kirch: The program that Dr. Pizzo described at Stanford [in the previous session] and the others you mentioned have been very high-profile and have gotten a lot of attention. But it's a mistake to believe that they are the cutting edge of how to manage interactions between industry and the teaching and practice of medicine. For example, many teaching institutions

long ago eliminated or severely restricted vendor interactions in the hospitals. What is significant about the Stanford position is that it has eliminated a very large number of small relationships but continues to allow a more limited number of large relationships. That's why I'm so enthusiastic about getting a broadly representative group of people to sit down and look at this issue of industry support for medical education—because the institutions you

mentioned have not established a consensus. They've taken some high-profile actions, and the profile derives mainly from their position in the community. But there are many other actions going on as well.

Ms. Totenberg: Are there penalties for not complying with the Association of American Medical Colleges (AAMC) code of ethics?

Dr. Kirch: The AAMC is the association that medical schools and teaching hospitals belong to. It is a parent of some of the regulatory entities—such as the Accreditation Council for Graduate Medical Education, which oversees residencies, and the Liaison Committee on Medical Education, which accredits medical schools—but it's only a parent of these bodies. At the same time, the AAMC does have policies that are established by its governing body, and I believe that these policies do set a bar. While AAMC policies may not have regulatory impact, I've been impressed that when the leaders from academic medicine who govern the AAMC agree on something, it is a hard-won consensus and it penetrates the field widely and effectively.

Will we end up with a system where the big fancy institutions have one set of ethics and everybody else has a different set?
—Ms. Totenberg

Mr. LaViolette: AdvaMed is in a similar position, being a voluntary association. We recognize the limits of our enforcement capabilities, but we have tried to create something to serve this purpose. So, in the process of disseminating the code of ethics, we opened it up to all members of the device industry, whether they are a part of AdvaMed or not. All members can have a license to the code, which requires meeting minimum certification and compliance standards and confers the right to promote adherence to the code through display of the AdvaMed logo. There are specific requirements to demonstrate compliance.

If a member, in good standing or not, were to violate the requirements, we would revoke its license. This would force the subject company to cease display of the AdvaMed logo, and it implies that basic compliance and certification standards are not in place. Increasingly, health care providers are asking vendors to certify code compliance. Failure to do so will have intensifying commercial implications in the future. So there is an effort to give the code some teeth, although it may not scare major corporations.

Ms. Totenberg: Does AdvaMed disclose license revocations publicly?

Mr. LaViolette: Yes, on the AdvaMed Web site.

Ms. Totenberg: Do you put out a press release?

Mr. LaViolette: We haven't reached that position yet, but it's something we might consider. I say that because the industry is very focused on credibility. To the extent that an individual member damages the credibility of the broader marketplace, that hurts everybody. So we certainly might look at taking on more aggressive disclosure of violations—or, if you will, incremental "enforcement" actions—over time.

Ms. Totenberg: Is there public disclosure at NIH when there is a violation of rules?

Dr. Ruiz Bravo: It depends on the violation and its nature. We have conflict-of-interest policies and rules, and while NIH itself is not a regulatory agency, it is in charge of implementing some of the regulations that have been passed down from Congress. When there are investigations, they are typically confidential until there is an actual finding of misconduct or something similar, at which time they are made public. But the finding of misconduct would be done by the Office of Research Integrity, not by NIH. There are very few such cases.

Question from audience: There have been a number of subpoenas from the US Attorney's offices in Philadelphia, New Jersey, Boston, and elsewhere in

recent years in response to questionable sales and marketing practices by drug and device companies. What impact have these subpoenas had on industry? I would like Mr. LaViolette to address this both from the general industry standpoint of the AdvaMed code and in terms of specific sales and marketing practices at Boston Scientific.

Mr. LaViolette: Any enforcement action sends a signal industry-wide of what the Office of Inspector General is interested in. At Boston Scientific we look at these actions and ask ourselves if our policies are clear, if we're acting in accordance with those policies, and if our policies need to change. Again, much of what we're talking about, at least as it relates to the AdvaMed code and ethical practice, is not legislated anywhere. We're therefore dealing with an area that transcends the law and is subject to interpretation. As a corporation, we're trying to have a degree of market equity that is above the norm. We're trying to act in a way that's respected and for the long term. Would we change our practices ahead of the industry? I would hope so. Would we then try to bring the industry along, for the greater benefit? The answer is yes.

Certainly, any set of subpoenas from the Department of Justice leaves a black mark. Do we work to prevent that? Yes. Do we work to prevent it just so that we don't get investigated? No. We work to improve so that we have a more productive system over time.

■ WHEN MEDICINE SOLICITS FUNDS FROM INDUSTRY

Comment from audience: I'm a leader of marketing in a privately held medical device company. I was pleased to hear Mr. LaViolette speak on behalf of the device industry because I was a bit troubled by this morning's discussion, which seemed to be moving toward a depiction of "big bad industry" that influences physicians. Many people in industry were thrilled with the development of the AdvaMed code of ethics because it provides an avenue for industry to walk away from some activities that we didn't necessarily want to do, such as providing free rounds of golf, sporting tickets, coffee cups, etc. Industry has an interest in diverting our marketing funds into education, but we find that physicians are getting more adept at marketing to us. They send a subtle message that our product might be pulled if we don't support an educational activity they're planning. It can amount to arm-twisting. AdvaMed and the industry are doing an effective job at trying to limit conflict of interest, in my opinion, but there needs to be

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increased vigilance on the physicians' side to limit their marketing to industry for funding.

Ms. Totenberg: Your comment brings to mind the subject of foundations that are set up by academic institutions or private groups of doctors to fund their research or their fellowships. Let me ask the panel, how much of this type of activity is appropriate?

Dr. Kirch: The world of foundations was essentially invented by universities to accomplish purposes that the university itself believed it could not accomplish. I would argue that in most cases it has helped universities carry out their missions. Every university I've been involved with has very clear guidelines about how foundations can and should be established, and how the oversight occurs. So the real issue here exists outside the academic research world, in settings where there isn't oversight by a parent institution.

Mr. LaViolette: At Boston Scientific we certainly see foundations routinely. They're prominent, they're everywhere. They're generally legitimate, and you can tell when they're not. At our company we have a clear segregation of responsibilities for the purpose of evaluating research requests. It's entirely separate from anyone aligned with business success or failure. We make very clear our requirements from a foundation in terms of what the request is and how the funds will be used; if the request is legitimate, we're more than happy to deal with foundations.

Ms. Totenberg: But it's not a question of whether the foundations are phony fronts. Let's say that Dr. X sets up a foundation because he or she can't raise money directly from drug companies or medical device companies. It's a foundation to fund fellowships in ophthalmology, for example. Various companies say, "Yes, we'd be happy to give you \$5,000 for that." Suddenly, all the fellowships in this department are funded by three companies who now have a special relationship with that department. These companies, quite naturally, might now say, "We have some new, cutting-edge devices that we'd like the hospital to look at seriously. It would be great if you could use them first on an experimental basis." It's not that anybody has bribed anybody. It's just human nature.

Mr. LaViolette: There's a difference between legitimate investments and inducements, and we all have to look at those subtleties. We all have to look at

whether there is a connection between a grant made historically and a request for business made today. To the extent that the request for business today is made entirely on the basis of the technology or product in question, it's perfectly legitimate.

Dr. Ruiz Bravo: Let me say a few words about the Foundation for the National Institutes of Health (FNIH). As I said in my presentation, it was created by Congress and it is distinct from NIH. That's an important distinction. Also, we have found the FNIH to be extremely helpful in terms of furthering the NIH mission in biomedical research. It is able to partner with industry and others, and NIH forms one part of that partnership. So it brings us together with industry in a way that facilitates our interactions.

Ms. Totenberg: How does it actually work? Does the foundation give money for research to NIH scientists?

Dr. Ruiz Bravo: No, the FNIH funds programs through donations. It can accept contributions and gifts, and there is a link on the FNIH Web site for contributions. The foundation doesn't have its own scientists or any intellectual property of its own. The foundation is probably most helpful to the NIH through the partnerships that it brokers. For instance, for the Osteoarthritis Initiative that I mentioned in my presentation, FNIH brought all the parties to the table to talk about how the initiative was going to work—which components industry would contribute, which components NIH would contribute, and so forth.

■ WHAT CONSTITUTES 'APPROPRIATE' INFLUENCE?

Question from audience: The panelists have talked about medical decision-making not being subject to inappropriate influences from industry. As a lawyer, my clients are always saying to me, "Don't tell me what I *can't* do; tell me what I *can* do." So I'd like to know what the panel considers to be appropriate influences that can arise from this relationship between industry and academe.

Dr. Kirch: I can't speak about the NIH policies, but I think that in academic medicine a wide range of interactions remain possible, accepted, and productive. Where the line needs to be very clear is when you get to the bedside, and whether influences are entering into the care of patients. Most of the regulations that I see being put in place aren't based on some abstract

goal of stopping interactions. They're simply trying to prevent the contamination of patient care.

Mr. LaViolette: A lot of things are permissible, but you can either be heavily involved in investigations or be heavily involved in invention. You can't really be involved in both. If a physician comes to my company and wants to be a lead investigator, that's great. And he will be paid fair market value for his services. If another physician comes to us with intellectual property, wants to sell us an invention, and wants to participate in the marketing side, that may also be appropriate. But we can't let one spill over to the other. So there are a lot of things that you can do, but you can't mix and match roles. Drawing clear distinctions is key: the inventors cannot be the investigators.

Dr. Ruiz Bravo: Dr. Pizzo put it best when he said earlier that you want to distinguish between interactions that are scientific and interactions that are related to marketing. The first should be encouraged, whereas marketing is something we shouldn't do.

Ms. Totenberg: How many of these research decisions are affected by the type of drug or device being investigated? Some may help a relatively small number of people, whereas others can make a university a lot of money if they pan out, like the statins. When I was first at National Public Radio, before we were as large a news organization as we are today, I thought that our coverage was skewed by who was giving us money. We would get grants from a foundation to cover mosquitoes in Africa, for example, when that might not have been a top coverage priority. We don't do that anymore; we have rules against it and big firewalls. But I can't help but wonder whether research decisions aren't similarly skewed when intellectual property can benefit large institutions so greatly.

Dr. Kirch: That's why the focus has turned toward institutional conflicts of interest, and why they are more difficult than individual conflicts of interest.

One of the things that worries me is the underlying premise in discussions like this that we've allowed an unholy alliance to develop between the private sector and the academic sector and that we need to unravel that alliance. I view it differently. Some of the debate needs to go back to our priorities as a nation and what we are and are not willing to support. For instance, the issue of industry support for fellowships was raised. Part of the problem is that the support for residency and fellowship education has essentially been static. In terms of need, it's actually gone down. Residency directors are scrambling to "cross-subsidize" their educational

enterprise. If we continue in current trends and decide that scientific discovery and the education of the nation's health care workforce are no longer public goods, why are we surprised if everybody works so hard to establish relationships with the private sector?

I'm especially concerned about the core of medical education. We have pushed tuition for medical students to its absolute limit. Every medical school in the country is scrambling to figure out ways to fill the gap without burdening those students even more and undermining society and its need for doctors. This is really an issue of societal priorities.

Ms. Totenberg: Has anybody asked the AAMC to testify about this before Congress?

Dr. Kirch: Not yet, but the AAMC's governing body believes that this is *the* issue we have to put on the table. A convergence of developments has brought us to this conclusion: real distress at a number of our member institutions, growing evidence that we face major health care workforce shortages, and indications that physician scientists are becoming an endangered species. There is a compelling list of warning signs, and we need to get that list in front of the nation.

■ WISDOM BEYOND ONE'S OWN WALLS

Question from audience: From the standpoint of institutional conflict of interest, where can academic medical centers turn outside our own institutions to regulate collaborations with industry that are taking place within our own walls? Also, if patients are asked to participate in a clinical trial within a university, do they have the right to know whether the university stands to profit from its participation in the trial? If so, should we tell them a dollar amount or an equity amount, or is a general statement in the informed-consent form sufficient?

Dr. Kirch: In both instances, the solution lies in making better use of people outside our institutions. There is wisdom beyond our walls that we don't tap sufficiently. One finding in AAMC's initial survey on conflicts of interest was that there was less use of public representatives on research review committees than we had expected.

With regard to patients, I am a great believer in the effectiveness of representatives who are designated not to represent the institution but to represent patients, be it in the consenting procedure or in other matters. And there's a corollary benefit: the more the public is involved in these processes, the more we recapture its trust.