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Panel discussion

Applications in the real world: Case studies in defining boundaries and managing innovation

Dr. Adkison: Once upon a time, the rules and roles in medicine and medical product development were clear. Biomedical faculty worked full-time in universities, business was kept outside the academic ivory tower, and the two worlds didn't mix very much.

Those times have changed, and we now live in a far more complex world. The Bayh-Dole Act has turned over technology generated with federal funds to the universities that develop it, with instructions to partner with industry and move it to the marketplace. Faculty entrepreneurs have developed relationships with industry, and industry has entered the halls of academe. This complexity has ushered in a host of conflicts and conundrums, but in the process, much new technology has been moved to the marketplace to improve health care.

The conflicts of interest raised by this complex current landscape touch all aspects of the mission of academic medical centers—clinical care, research, education and training, and administration—as has been made abundantly clear by the earlier portions of this conference.

This panel discussion will attempt to bring today's discussion down to a practical level by exploring two case studies that spotlight specific challenges involved in managing potential conflicts that might arise from close interactions between industry and medical centers and their faculty.

Dr. Cassell reported that she receives a salary, grant/research support, and stock options through her employment with Eli Lilly and Company. Dr. Stossel reported that he has ownership interests in ZymeQuest, Inc., and in Critical Biologics Corp.; has intellectual property rights in Critical Biologics Corp.; has received consulting/advisory fees from Merck, Inc.; has received honoraria from Pfizer, Inc.; and has received royalties from Lippincott Williams & Wilkins. All other participants reported that they have no financial interests, relationships, or affiliations that pose a potential conflict of interest with this article.

Case study 1: Dr. Tunnel and DeviceX

Submitted by Michael J. Meehan, Esq.
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Dr. Tunnel is an employed staff surgeon at Royalty Medical Center. He is also a consultant for DeviceX, Ltd., a company that manufactures medical devices. Dr. Tunnel receives \$25,000 a year from DeviceX for consulting on a variety of surgical devices. Royalty Medical Center purchases products from DeviceX, and Dr. Tunnel uses DeviceX products in his surgical practice. He currently conducts no research that is sponsored by DeviceX.

If Dr. Tunnel plans to implant Food and Drug Administration (FDA)-approved DeviceX products in his patients, should he disclose his consulting relationship to his patients?

Dr. Kahn: I believe that the need for disclosure depends on whether FDA-approved choices other than the DeviceX product exist. If there are no other approved devices, then he shouldn't necessarily have to disclose. But if there are, then the answer is yes, because he has a financial stake in the use of a particular product.

Dr. Pizzo: Let me put you on the spot and ask you to put yourself in the shoes of the patient. How would you then answer the question?

Dr. Kahn: If I were the patient, and Dr. Tunnel said that he wants to use the DeviceX product and that he has a financial relationship with DeviceX, I would ask him if there were other choices besides that device.

Dr. Pizzo: Dr. Tunnel may argue that he's not doing research on this device and that it's FDA-approved, so there is no reason to make a disclosure. And that may be appropriate. On the other hand, if you're the

patient, suppose that you have a complication or later discover that Dr. Tunnel did have financial stake in this. You might wonder why Dr. Tunnel did not disclose his stake. If your goal is to ensure trust, it seems that there ought to be disclosure.

Dr. Stossel: There is no harm in disclosing anyway; it seems like an easy thing. Ezekiel Emanuel at the National Institutes of Health (NIH) did a study of more than 250 patients in cancer trials in which the patients were asked if it mattered to them if their doctors had a financial stake.¹ The answer was overwhelmingly “no.” This question was asked numerous ways, involving stock, stock options, equity, cash, and others. To each, the patients said that it didn’t matter. They were also asked if they thought that a system for oversight existed. They did think that there was such a system. The question that wasn’t asked is if the patients would still not care even if there was no system for oversight.

Dr. Cassell: I side with Dr. Pizzo; in the interests of disclosure, transparency, and enhancing and building trust, I advocate informing the patient. To me, it wouldn’t make any difference if it were the only FDA-approved device. The question is whether it’s better to have that product or no device implanted at all. There is still opportunity for bias and conflict regardless of whether the product has regulatory approval.

Comment from audience: I’m a surgeon, and I can tell you that this practice is not limited to academic medical centers. There are many community hospitals in which an orthopedic surgeon will be asked to become a “consultant” to a device manufacturer, which may mainly consist of asking him to complete a compensation form with his Social Security number. He is paid a substantial amount of money—I doubt any of them would do it for as little as \$25,000—and it is linked to the use of certain prosthetic devices. As far as I know, in the real world those disclosures are not made to patients before the prosthesis is implanted.

Dr. Pizzo: Do you think they should be?

Same audience member: Yes, the relationship should be explained and the patient should be given credit for having the intelligence to sort it out. In cases in which the relationship with a company is legitimate, I think that will usually be quite clear to the patient. Some may even seek out a specific physician because he or she is recognized as an expert in the design of a particular device.

Comment from audience: The NIH survey of cancer patients that Dr. Stossel cited might be much less conclusive than it seems in that many of these patients face dying very soon. Do you think that the same overwhelming percentage that said that it’s all right would have said so 5 years before they got the cancer that is threatening their life?

Dr. Cassell: The same question occurred to me. It would be helpful to do a similar study in other patient populations and ask the follow-up question that Dr. Stossel mentioned. That could be quite valuable.

Dr. Stossel: When I was a medical student I was taught that there’s a conundrum. If you’re the type who likes to explain everything, some patients will appreciate being well informed, whereas others may think that you don’t have any confidence in what you’re doing or that you’re wasting their time. It’s not a one-size-fits-all proposition.

Dr. Pizzo: I agree; you have to adapt the information that you’re providing to the patient based on what he or she is willing to receive. At the same time, you do need to be transparent and at least offer the information, and then you can add the details based on the patient’s interest.

It would be fascinating to do the study that you proposed, but as a pediatric oncologist I find that patients, and particularly families, are very willing to accept experimental therapy when they think there is no other option. Even if you tell them that it’s a dose-finding study with no known benefit, the likelihood that they’ll sign up is still very high because of the fear and desperation that are part of their dilemma.

■ NEXT LAYER OF THE CASE: WHAT ABOUT OFF-LABEL USE?

The FDA approves devices for certain specified uses. If Dr. Tunnel now wants to implant DeviceX products in his patients for off-label purposes, should he disclose his consulting relationship to his patients?

Comment from audience: In addition to giving information to the patient about the consulting relationship, it’s extremely important in this scenario that Dr. Tunnel make clear what off-label use means and what implications it has for the patient in terms of risk and benefit. I agree that it’s a discussion tailored to the patient’s level of understanding and willingness to hear the information, but it’s a crucial additional element.

Adapt the detail of the disclosure information that you provide to the patient based on what he or she is willing to receive.

—Dr. Pizzo

Dr. Adkison: What if the patient is counting on insurance payments? Does that make a difference?

Comment from audience: It does when the off-label uses are for diseases for which there are no research studies. There are many studies for common disorders such as osteoarthritis and lymphoma, but for very rare disorders you often have to resort to off-label use with the best available tools.

Comment from audience: I'm an orthopedic surgeon, and I've found that patients come in having already searched physicians' names on the Internet, where they can easily see a lot of our relationships with industry. For instance, information about many medical meetings is available online. Patients appreciate the dialogue. They often ask about these issues before we have a chance to raise them ourselves. If you have a frank discussion with your patients and tell them why you are doing exactly what you are doing—on-label, off-label, the issues that are raised, relationships—they appreciate it. They typically just move on to the next topic, which usually is how long they will be in the hospital.

■ NEXT LAYER: TECHNOLOGY LICENSING AND AN EXTENSIVE CONSULTING CONTRACT

Dr. Tunnel has conceived a special drug-eluting stent that could be deployed by a highly skilled surgeon to deal with challenging arterial anatomy or disease. Dr. Tunnel has worked with Royalty Medical Center's office of technology transfer, and the stent technology has been licensed by Royalty, as Dr. Tunnel's employer, to DeviceX. DeviceX would like Dr. Tunnel to oversee the early development of the research involving the stent that he conceived. DeviceX has sent him a consulting contract that proposes the following terms:

- Dr. Tunnel will convene an expert panel to meet twice and help design the research, including both animal and human trials, at a compensation of \$20,000 per meeting.
- Dr. Tunnel will lecture at two national conferences to discuss currently marketed DeviceX products for a fee of \$10,000 per conference.
- Dr. Tunnel will generate a review article discussing any DeviceX product that is already FDA-approved, for a fee of \$10,000. If he does not have time to develop the article, DeviceX will assist in the writing.
- If Dr. Tunnel satisfies all of these elements in 12 months, he will get an all-expenses-paid trip to the Cayman Islands for two persons.

Is the proposed consulting contract problematic? Should

Royalty review the consulting agreement before Dr. Tunnel is allowed to sign it?

Comment from audience: In this case, you could say that the inducements are excessive. Certainly the trip for two persons violates AdvaMed's code of ethics and all the other guidelines that we currently abide by. How do you manage the conflict? At my institution, we don't do research and consulting at the same time.

Dr. Pizzo: The issue of ghostwriting has come up at Stanford, and I was shocked by it because engaging in it violates every dimension of scholarship. At the most minimal level, my view is that if someone does it, that article should not be on his or her curriculum vitae. It seems to me that if you're a scholar working in an academic environment, you're going to want to do your own writing, not have someone do it for you, and you're going to want to examine the data and not have someone give it to you and then have you publish it. Otherwise, you're just behaving as a tool.

Dr. Stossel: I'm curious how widespread the use of ghostwriters and similar practices really is. Assuming that it goes on, how prominent and truly scholarly are the people who are doing it? You cease to be an opinion leader if

you're perceived as a shill for a company. I don't know who these people are.

Comment from audience: Being asked to lecture at national conferences to discuss a company's product is a very common experience for many faculty, especially because they are experts in the topic and it may be looked upon as expert information from an active clinician and researcher. The problem with a lot of these consulting agreements is that they don't discuss and carefully lay out who controls the content, the content itself, and the context in which the physician will be asked to deliver it, including all of the presentation materials that will surround the presentation and the introduction that will precede it. These factors will determine whether it is perceived as a genuine and legitimate scientific presentation or as a marketing presentation.

Dr. Kahn: This is getting awfully close to selling one's position; you have this supposed expertise and are taking money to speak as if you're independent when you're not. One would hope that the system would be self-regulating and that those people would cease to

You cease to be an opinion leader if you're perceived as a shill for a company.

—Dr. Stossel

be opinion leaders. The problem is that these kinds of relationships aren't disclosed, so there isn't a way for even their peers to know that this is what these people are engaged in.

Dr. Pizzo: Consider the good side for a moment. Someone is involved in carrying out a certain area of research and has tried to do it in a thoughtful way. Funding has come to them, in this case from industry. They want to share the information. I don't find that to be a negative as long as the disclosures take place.

Dr. Kahn: It depends on who controls the content; that is the crucial piece. Also, \$10,000 to give a lecture is a lot of money, and maybe that's a tip-off that it isn't quite as legitimate or defensible as it might be.

Dr. Stossel: It's very discipline-dependent. At the annual meeting of the American Society of Hematology, there are corporate-sponsored symposia that take place the weekend before the meeting. They're very popular because the practitioners are available to attend over the weekend. In my opinion, these symposia are of very high quality. For example, one symposium might be on anticoagulation in a broad sense, leaders in the field of anticoagulation will deliver the lectures, and the sponsor's product may or may not be mentioned. I think it's a win-win. If \$10,000 is the going rate, so be it.

Dr. Pizzo: I agree that the setting is really important. The American Society of Hematology does do outstanding educational programs, and anyone speaking there is going to be objective and stay focused on the primary topic. But if you translate that to a grand rounds or to a dinner event that residents have been invited to, that's when it gets confusing because the checks and balances are gone. The speakers are not before their peers, they're not particularly worried about their reputations, and if you look at the list of people who are lecturing at those sessions, they're not necessarily the thought leaders. They're often people who are simply willing to take the money to give those talks.

Comment from audience: Usually, the speaker discloses either in a consent form, in the conference, or in the paper that he or she has a conflict. But wouldn't it be much different if Dr. Tunnel disclosed that he was getting paid \$20,000 to give the two addresses? That information is never available. The landscape would change quite a bit if the amount had to be disclosed.

Dr. Adkison: That's a good point. A disclosure that

just says, "I have a financial relationship with the sponsor of this research," is perhaps not enough. A disclosure that says, "This company paid me X dollars to do such and such," is a better disclosure because whoever is reading the paper has more information on which to evaluate a bias or lack of bias in the paper.

Let's turn now to the other aspect of this latest layer of the case: the university has licensed Dr. Tunnel's technology to DeviceX, and now DeviceX wants him to oversee early development of the research and write protocols for the animal and human trials. Should Dr. Tunnel participate in designing the trials? What factors should be considered? Does it make a difference that he'll be paid to design the protocols?

Comment from audience: If one adheres to anything like the Association of American Medical Colleges (AAMC) recommendations for individual conflict of interest, Dr. Tunnel has already exceeded the level of income beyond which he should be presumptively prohibited, or have to demonstrate against a rebuttable presumption, from even participating in the design of the study. The argument by the AAMC is that even participating in the design is participating in human subject research. I'm curious how the panelists react to the AAMC standards that many of our institutions have adopted in one form or another.

A disclosure that says, 'This company paid me X dollars to do such and such,' is a better disclosure.

—Dr. Adkison

Dr. Stossel: I think there's a difference depending on whether it's a device or a drug being investigated. In this case, Dr. Tunnel is the guru in the use of a device that may not be ready for very widespread use at this point in its development; that may argue for his involvement in the study design. It's different with drugs, however, because it's not just a matter of ethics, it's a matter of common sense that a company would want to get as much replication and as much input into their technology as they can, so farming out the research and study design just seems like a commonsense approach.

Dr. Kahn: I was part of the AAMC task force that crafted the recommendations that were mentioned. The audience member is correct that there's a presumption that when a person has a level of financial interest over a certain dollar or equity amount, he or she has to make an affirmative case for being involved in clinical research, as opposed to someone else having to argue why that person should be excluded. We did point out that there are cases in which the individual has unique expertise, which is more likely to be the case in a device setting than in a drug setting.

Dr. Stossel: To be the devil's advocate, exactly what problem are we solving? Inventors don't design studies so that people die or to make their devices look as dangerous as possible; they want their devices to succeed. The assumption is that inventors are going to lie, cheat, and steal, but you could just as easily argue that they are going to bend over backwards to figure out how to make their product safe and effective.

Dr. Pizzo: This device-drug distinction is something we take into account at Stanford. We are much more willing, at least in the first phase of clinical trials, to recognize that the person who invented a device has the greatest capability, and therefore we may allow that person to be engaged in initial testing. By necessity, though, involvement has to be limited because the success of the device and the procedure will have to be extrapolated beyond that one surgeon.

Dr. Stossel: To show how crazy the rules at Harvard Medical School are, not only can I not participate in the design of a clinical study, I can't even be an author of a paper about my own technology.

Dr. Adkison: Any company whose long-term strategy is to market drugs and devices that are based on biased studies is seeking to cut its own throat because lawyers will eventually find out and come after the company.

■ NEXT LAYER: WITH EQUITY OWNERSHIP, HOW TO MANAGE INSTITUTIONAL CONFLICT?

As mentioned, the stent technology was licensed by Royalty Medical Center to DeviceX. In return, Royalty received 20% of DeviceX's outstanding common stock, a percentage of the stent's future worldwide sales, and two seats on DeviceX's five-person board of directors, one of which is held by Dr. Tunnel.

Should Royalty Medical Center adopt a conflict management plan that deals with Royalty's purchase of DeviceX products? Who should formulate and implement the plan—ie, who is sufficiently distanced to set up the institutional policy and deal with the individual and institutional conflicts of interest?

Dr. Adkison: I'll address the first question, since it's a straightforward one. Because Royalty now owns equity in DeviceX, it should definitely have a conflict management plan that provides some way of keeping its purchasing decisions at arm's length or that stipulates that Royalty will not purchase from DeviceX. How about the second question—who has the institutional responsibility for implementation and oversight?

Dr. Pizzo: I suspect that different institutions have

approached this in different ways. At Stanford, institutional review board (IRB) and conflict-of-interest oversight comes through the university, and so the dean of research or the vice provost of research is the person charged with that. That oversight is separate from the schools and provides an extra layer. The office of technology transfer is also not in the purview of the school of medicine but rather of the university. So there are firewalls that help in that regard.

Dr. Adkison: In this scenario, the equity is owned by the university, not by the school of medicine. In this case, who oversees the institutional conflict?

Dr. Cassell: Oversight by the board of trustees is not a bad idea, especially if you have a subcommittee that deals with these issues. Having served a year on the board of trustees at the University of Alabama, I believe that those boards have the expertise to deal with this type of oversight.

Dr. Adkison: The board of trustees is one suggestion. We also hear a lot from the AAMC about the importance of involving external people.

Comment from audience: I would like to digress for a moment. Although Dr. Tunnel is violating a lot of principles of ethics, what education did he have to fall back on? Often there is no curriculum in postdoctoral studies to teach research ethics. Nor was there necessarily an ethics curriculum during medical school or his surgical residency. The relationship he has with his patients is not a relationship of equals, but the ethical principle of coercion probably wasn't part of his boards. Even today, basic ethical principles are not a part of some medical curricula in the United States.

Dr. Adkison: Absolutely. We have a responsibility in our institutions to educate our students, our trainees, and our faculty in research ethics and medical ethics.

■ NEXT LAYER: DO THE INSTITUTION'S VARIOUS OVERSIGHT BODIES SHARE DISCLOSURE INFO?

The licensing agreement for Dr. Tunnel's stent also provides that Dr. Tunnel will personally receive \$10,000 upon achievement of certain milestones. One such milestone is surgical implantation of the stent in five dogs. Royalty Medical Center operates an animal facility where Dr. Tunnel could perform this, if approved, and Dr. Tunnel applies to Royalty's institutional animal care and use committee (IACUC) for approval to do this research.

How would Royalty's IACUC learn about the personal and institutional financial interests that lie behind this proposal? How would the conflict-of-interest committee know

that Dr. Tunnel has applied to do this animal research? What kind of mechanisms are in place?

Should Royalty permit Dr. Tunnel to conduct the dog surgeries in Royalty's own animal lab as opposed to using the lab and lab personnel of another facility?

Dr. Adkison: Many institutions have a practice or policy requiring review of all the consulting agreements that their faculty enter into and requiring shared files, databases, or some other mechanism for cross-checking. I believe that NIH regulations also require that the principal investigator certify potential conflicts or lack of conflict on the cover sheet for routing a proposal. If a potential conflict of interest is recognized, it goes to the conflict-of-interest committee.

Comment from audience: Our ideas of conflict of interest in the area of animal research or basic research are far less developed than those in human subject research. I'm the research compliance officer for a hospital, and the institutions that I've been involved with either don't have a transactional disclosure for animal or basic research, except if an NIH grant is involved, or are just beginning to have that kind of disclosure. Dealing with these issues in the area of animal research is a new endeavor at most institutions.

Dr. Adkison: Yes. The responsibility that federal regulations have placed on universities is not only to safeguard patients but also to protect against biased data, which presumably could arise from either animal or human research.

Question from audience: What if the question of licensing weren't involved in Dr. Tunnel's case? What if he was the inventor and was doing this research—so therefore the same skill set would be involved—but the financial conflict wasn't a key part of it? Does the financial conflict so affect our perception of what the results will be that it prevents us from allowing something that we would otherwise permit?

Dr. Stossel: You raise a good point. I have been doing research for 35 years, and I have never been subtly biased—I have always been totally biased. You have to be totally biased because on most days, things don't work and you need to overcome failure. It's a conceit to think that we're sanitizing research and that financial interests are worse than any other kinds of interests, such as promotions.

Comment from audience: My doctorate is in social psychology, and I think a key point has been omitted. There are many experiments showing that money and other inducements can change what people think,

what they believe, what they are willing to do, and even what information they pay attention to. At the same time, there's a ton of evidence that says that in most cases, we can't say what we are influenced by. In experiments time and time again, one group of people is influenced while another is not. You can ask the people who were influenced, "Did this influence change your opinion?" and they all say "no."

Dr. Stossel, many of your comments seem to ignore that the truth may be altered and patient care may be altered when these inducements get one to do things and think things that he or she wouldn't otherwise do or think.

Dr. Stossel: All I'm saying is that financial inducement is just one of many inducements. Why not get rid of them all? Of course, we can't do that. That's why I keep coming back to track record. I didn't mean it to be *aggregate* track record, which is a point Dr. Kahn raised in his presentation, but *individual* track record.

Dr. Pizzo: In my presentation, I mentioned career development and promotion as other conflicts, and I agree that they are very much a part of this process. That said, there is a weight to financial inducement, and you can see it influence behavior in so many different ways. Clinical faculty respond to incentives to do more relative value units, so there is a response to financial inducement.

You're saying, "Trust me—I'm Tom Stossel, highly recognized academician. I would never do anything wrong." I've known you for 35 years and I trust you, but that's not the issue because the public doesn't know you. Not everybody is necessarily going to follow the same pattern that you might. Not everybody is worthy of being trusted, regardless of what they may say.

Dr. Stossel: I'm not saying, "Trust me." I'm saying, "Don't trust me. Mistrust me. Be skeptical." Just because something is published in a prestigious journal doesn't mean it's true. All I can say is that, on balance, I try as best I can to be honorable but I'm going to make mistakes and, as I said, I am biased.

Dr. Pizzo: You say that being involved in research creates bias; I recognize that. But you are also saying that we don't need guideposts or regulations because at the end of the day, everything is based on personal trust. That's what I disagree with. I'm not for overregulation by any means, but I am for having certain standards so that people at least recognize the boundaries. In their absence, we would have organizational chaos.

Dr. Stossel: I couldn't agree more. We have speed limits, but we don't take people's cars away for speeding. We

catch them when they're speeding, we fine them, we imprison them for drunk driving. That's where I think we should be; I'm not advocating a free-for-all or chaos.

Comment from audience: As a prospective patient, every time the conversation leads to disclosing financial ties to patients, I get queasier and queasier. As a prospective patient—and an educated one at that—the sicker I get, the less capable I will be of evaluating disclosure information and the less interested I will be in doing so. I want to be able to trust. I am capable of doing the research but I don't want to do it; I want you to do it for me. It scares the hell out of me that you want to put the responsibility on me, when I'm at my sickest, to decide whether you are ethical and your concerns are compatible with my concerns.

■ NEXT LAYER: SHOULD THE INVENTOR BE INVOLVED IN HUMAN TRIALS?

Dr. Tunnel completes his animal research. In doing so, he has personally developed a new and unique surgical technique for using the stent under challenging anatomic conditions. He's eager to begin clinical trials with human subjects. DeviceX applies to the FDA for an investigational device exemption, and it is granted. Dr. Tunnel applies to Royalty's IRB for approval to conduct a single-site, phase I clinical trial involving five human subjects.

Should Royalty permit Dr. Tunnel to conduct this clinical trial in humans in Royalty's own hospital?

Dr. Adkison: I think the essence of this question is whether there are times when the unique skills required to test the device should override the rule that the conflicted investigator can't be the principal investigator in a clinical trial. Your thoughts?

Comment from audience: I think Dr. Tunnel should be allowed to do this because he has to work with his team. Surgery is not a one-man or one-woman deal. You have a team, you have equipment, and you need to see if the technique works; it's a high-risk technique. If I were on the IRB, I would have a great deal of difficulty with his financial conflict of interest, but I still think he should be permitted to do it. Yet it has to be transferable to other surgeons; otherwise it's pointless. He could do it on five patients and then train others to do it.

Dr. Stossel: A good historical example is hyperalimentation. In the early days, the physicians who developed this breakthrough technology had to live in

the hospital with the study patients, and the surgical team was up all night. You could never farm out a procedure like that until it became somewhat established.

Dr. Pizzo: Today at Stanford, we would do precisely that in a situation in which the technique was unique, still under development, and there was no expertise aside from the person who developed it. So at a very early phase, with oversight, we would let that happen.

Dr. Adkison: Dr. Pizzo, would you allow Dr. Tunnel to select the patients and obtain their consent?

Dr. Pizzo: No, we would not allow that.

Comment from audience: There may be some theoretical circumstances in which it would be okay for Dr. Tunnel to go ahead with this, but ultimately we're not

trying to develop a product, we're trying to find the truth to a question. Two things characterize good research. One is equipoise, which is an uncertainty about the answer to the question being asked. The other, which we have talked about, is not having a stake in the results of the research. I think this case violates both of these principles: there is a clear stake in the results here, and it is hard to imagine that Dr. Tunnel would have equipoise in finding out whether this device works or not. Simply disclosing these relationships to sick patients, as has been pointed

out, isn't enough. I would vote for not having this person do the research simply because there can't be equipoise and there is a clear stake in the results.

Dr. Adkison: And if Dr. Tunnel doesn't do it, it doesn't get done; you're comfortable with that?

Same audience member: There are some circumstances in which an IRB might determine that this must go forward because of some compelling reason why it cannot be done any other way, but I certainly would look for some other way, and then have others analyze the data, select the patients, obtain patient consent, and so on.

Comment from audience: I take exception to characterizing the outcome in this case as the research not being allowed to go forward if Dr. Tunnel is not allowed to participate. I'm affiliated with hospitals in the Boston area that are under the Harvard rule system, under which Dr. Tunnel's arrangement would not be allowed. Those rules wouldn't allow him to participate in this

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—Comment from audience

research *because he has chosen to have a financial interest*. The ideal solution would be to put the onus on the physician to make a choice between continuing the relationship or being involved in the research. He works in an academic medical center, so he can do the research, but he can't do so and at the same time be in a position to make a lot of money from it.

Comment from audience: A phase I study of a device is not intended to prove efficacy; it is undertaken in fully informed patients—and that includes conflict-of-interest disclosure—to rapidly understand the technique and to discover any changes in the device that might be necessary for progression to phase II.

This very complex problem of a physician inventor using his own device has been explored in a landmark paper by Dr. Richard Popp of Stanford.² That article discusses the oversight that is needed in this very special circumstance and also how to manage as early as possible the handoff from the expert investigator to a second set of nonconflicted investigators.

Dr. Adkison: Let's move on to another case study. Unfortunately, time won't allow us to get into all of its layers, but it's worth consideration because it raises a different kind of conflict of interest that institutions need to deal with.

The onus should be on the physician inventor to choose between continuing the relationship with industry or taking part in the research.

—Comment from audience

Case study 2: Dr. Parker, the junior colleague, and the start-up company

Submitted by Claudia R. Adkison, JD, PhD
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Dr. Parker is chair of a clinical department in the school of medicine. She collaborates with a tenure-track assistant professor in her department, Dr. Adams, on an NIH-funded research project that results in an exciting novel compound with substantial promise as an important therapeutic drug. The university files a patent on the technology.

Is the collaboration between Drs. Parker and Adams a conflict of interest? If so, what kind? Should any safeguards be put in place?

Comment from audience: There clearly is a conflict of interest between the assistant professor and the chair because the assistant professor, being on a tenure track, has to do what the chair says.

Dr. Adkison: Yes, so this is an administrative conflict. As far as safeguards that might allow this collaboration

to go forward, something that has been tried, although with only moderate success, is to have all decisions concerning this tenure-track investigator—salary, allocation of space, promotion, and tenure—assigned to another chair in a similar department. This arrangement works at the initial level, but it can get dicey when the collaboration gets more complex, as we will see.

■ NEXT LAYER: THE START-UP COMPANY

The compound requires further research and development to make it attractive for licensing by a large pharmaceutical company, but funding for this additional research is not available from the NIH or the university.

Drs. Parker and Adams propose to form a start-up company, TheraRx, and ask the university to license the technology to their start-up company. The school of medicine has a policy that requires all such start-up activities to be approved by the dean's office and the office of technology transfer, and it also gives the university the right to take a reasonable amount of equity in the start-up company if it chooses. The school takes 20% equity in TheraRx. Drs. Parker and Adams fully disclose and seek approval, which is granted.

Should the school of medicine allow a chair to form an external company with one of its faculty members who reports to that chair? If so, should a management plan be put in place? What elements might suffice?

Dr. Cassell: Having been a former chairperson, and a research-intensive one at that, I think this arrangement should be allowed so long as appropriate oversight mechanisms and safeguards can be put in place and both investigators are fully informed of the consequences if they break them. In many cases, the chair can serve as the best role model for appropriate behavior. I realize that I'm biased, but I think it would be wrong to exclude the chair or the junior faculty member from this opportunity. Both could be protected by appropriate safeguards.

Dr. Adkison: Let me be the devil's advocate and point out that a department chair is an institutional official, and one could say that she should be held to a higher standard in terms of conflict of interest.

Dr. Cassell: I think that's true, but as long as the boundaries are defined, and as long as they act within those boundaries, they should be allowed to participate.

Dr. Stossel: I agree. University presidents, deans, and

department chairs are on boards of major corporations and receive stock or stock options from those corporations. Is a start-up company somehow unsanitary compared with those companies?

Dr. Adkison: Often the corporations on whose boards those university officials serve have no relationship with the university—they are not vendors to the university and do not sponsor research there.

Dr. Cassell: Dr. Pizzo, would Stanford allow this type of scenario?

Dr. Pizzo: Yes, under the right supervision, this type of partnership could be allowed.

Comment from audience: I'm sure that your hypothetical medical school has a mission of disseminating knowledge and caring for the sick. There is no NIH funding at this risk level and industry doesn't want to fund it either. If you're going to hold your leaders to a higher standard, what higher standard can there be than to tell your leadership to take this forward the only way it possibly can?

■ NEXT LAYER: SHOULD THE UNIVERSITY TAKE EQUITY?

The compound has great potential for use in treatment of disease. With this in mind, should the university take an equity position in TheraRx? What might be the downstream consequences?

Dr. Cassell: Yes, as long as the appropriate safeguards are in place.

Dr. Adkison: What are those appropriate safeguards?

Dr. Cassell: One would be total independence of any group responsible for the oversight. Another would be ensuring that you have the expertise in place to detect problems that might arise. These are two safeguards that initially come to mind.

The University of California system has made a conscious decision to take developments or discoveries much further before they license them to larger companies. Allowing the university to take equity in a company could be a tremendous teaching tool, in addition to providing a valuable source of income.

We've reached our limits in the amount of money that can be brought into universities through tuition and also possibly from state and federal funding. Universities have to look at other ways to generate income. We need to remain competitive in this area as a nation when you consider that the governments of all of the United States' technological competitors

are increasing their investments in basic research. Even Japan, as rigid and as cautious as it has been, has now set aside Ministry of Health money to promote interaction between academia and industry. The whole world is changing, and while we need to maintain a scholarship role for universities, we also have to make them a more integral part of economic development. Otherwise, I think we'll lose all around.

Dr. Pizzo: It is easiest to outsource development related to engineering or information technology, but it gets more complicated when there is a potential clinical trial involved, because that's ongoing research that involves patient care. Certainly, in the early phase, the university can be involved, as you've articulated, Dr. Cassell. But at Stanford, we divest our equity in a start-up company if a clinical trial of that company's product goes forward at Stanford. That is how we would draw the boundaries.

Dr. Stossel: In her presentation, Dr. Cassell mentioned the tension between institutional and individual ownership of start-up equity. One reason to keep ownership at the level of the faculty is that it can pay off even better in terms of future philanthropy to the university from faculty members with successful inventions.

Dr. Pizzo: That was Stanford's philosophy with regard to engineering. It didn't ask faculty for gifts; instead, philanthropy has been spawned from Silicon Valley, with faculty who have returned and contributed considerably to the university. This hasn't yet happened in the biomedical area, but perhaps it will over time.

Dr. Cassell: This brings up another point: industry-academia interactions have been much more common and much larger in scope in the physical sciences, including engineering, and even in business disciplines, in terms of consulting and the like. These fields have managed to either keep it from public attention in the media or else they have managed it very effectively. We need to look closely at how these fields have managed their interactions with industry.

Dr. Pizzo: I agree, but probably the key difference is that human subjects are not involved in those fields. When human subjects are involved, it gets muddy.

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