The Crisis in Clinical Research: Panel Discussion II

Alan Buchman, MD, MSPH, Barry Gertz, MD, Timothy Lipman, MD, and Kevin Schulman, MD

Key Words: clinical research

Dr. Alan Buchman (Feinberg School of Medicine at Northwestern University): Dr. Klein?

Dr. Samuel Klein (Washington University School of Medicine): With industry looking for new sources of support and revenue to generate research and develop new products and with academic medicine looking for new sources of revenue to maintain their clinical research infrastructure, a collaboration between the two, which is not currently the case, would benefit everyone. This collaboration, however, must be established within the ethical guidelines of conflict of interest and bias. So, should we explore closer collaborations through which industry and academics develop real partnerships of working together in which trials, drug development, and various phases of studies can be done with greater ease within different institutions and in a manner that can be supervised and make everyone happy regarding its ethics and conflicts?

Dr. Buchman: Dr. Gertz?

Dr. Barry Gertz (Merck & Co., Inc.): I do think such a collaboration is possible. Such partnerships are happening at various levels. As I mentioned, these consortia that are growing in numerous places are collaborative efforts across government, industry, and academic groups. Soon, we will hear reports about those efforts. In addition, industry and academic research are already successfully collaborating, for example, the Academic Research Organizations (ARO), the Timi Group, and the Duke Clinical Research Institute have collaborated and the Oxford Clinical Trials Group in England have arranged projects in which they are collaborating and funding research. These organizations have moved into issues of general health-related questions that can be built into the trial. We need to explore these mechanisms.

Dr. Buchman: Dr. Davis?

Dr. Pamela Davis (Case Western Reserve University): We can create collaborative relationships between industry and academics. We need to build in appropriate safeguards, but we can accomplish this. Coming from the cystic fibrosis world, I have a different perspective. Regarding cystic fibrosis, big pharmaceutical companies are not interested in this disease, which affects 30,000 people. The Cystic Fibrosis Foundation (CF Foundation) has taken a leading role in supporting basic research and convincing the National Institutes of Health that the organization wants to support research that the CF Foundation has catalyzed but also in developing a therapeutics development network that makes rapid-fire clinical trials feasible for industry so the CF Foundation and industry can establish that relationship. The federal government could participate in this collaboration because ultimately, the discoveries must be brought to the public, and the root to the public is the private sector. So we need to partner academics and industry, but we also need to involve voluntary and federal funders, which might elevate or abrogate some issues of conflict of interests.

Dr. Buchman: Dr. Schulman?

Dr. Kevin Schulman (Duke Research Institution, Duke University School of Medicine): At the Clinical Research Institute at Duke University, we have formulated ideas that a group of people exists who want to abdicate all industry connection. However, if we are concerned about industry and we don’t partner, we can never address our concerns. Therefore, we are building a relationship in which we present transparent rules of governance and move forward, and we are succeeding in our partnership. We just published a paper, which the sponsor did not like, but we had agreed previously to go forward and publish.

The biggest conflict of interest I have seen was in a National Institutes of Health clinical trial that we published. In the study, we had to face not a financial conflict but an academic conflict of interest; the conflict spurred how we shaped the paper’s discussion, and the people were more vehement than any industry representatives.

Dr. Buchman: Yes, we must consider that conflicts of interest are not just issues between industry and academics but also within academics. I wrote a letter on conflict of interest within academics, namely, those involving competing ideas when they come to a head during manuscript or grant application review. These types of conflicts are not normally identified. Only the Annals of Internal Medicine was willing to publish the letter. My experience illustrated the issue of conflict: that when one submits an article for publication, two people can determine whether the results will affect patient care. If those two reviewers like the article, the journal publishes it. If they do not like the article, the journal does not publish. Two people decide—perhaps the editor looks at their reviews—but if those two reviewers have a competing research idea or they do not agree with your approach, then you must submit your research elsewhere. In so far as grant review goes, most of the committee never review a given grant—the review is primarily undertaken by two, although sometimes a few additional reviewers. Peer review is beneficial, but it is also flawed.

Judy Jones (Cutaneous Lymphoma Foundation): I am from the Cutaneous Lymphoma Foundation, and I am directing this question to Dr. Gertz, but anyone can answer: Where do you see the role of the patient in this process?

Dr. Gertz: The patient has a role in multiple parts of this process. We conducted a study of cutaneous lymphoma, and we worked with an organization. We needed to identify an effective molecule through trials and get our findings out for
patients but for a small group of patients who were in need. In that case, we try to reach out to those organizations. The patient has more of a voice, particularly if they view a risk as acceptable compared to the benefits to the patients’ quality of life. We need to hear the patients’ voices more frequently in the latter situation.

Judy Jones: What if we broaden the partnership beyond patient advocacy groups to the general population, which may not understand clinical trials?

Dr. Gertz: We need to educate the population. We are meeting today because we all believe we need to inform people of how important health-related research is to their ultimate well-being and to help them understand, for example, how drug safety issues affect them. We need to better educate the public and remove the high level of noise that frequently circulates around health education.

Dr. Buchman: Dr. Lipman?

Dr. Lipman: In terms of patients, subject participation is key and yet also problematic. I am not at risk for breast cancer, but a number of my family and friends have had breast cancer. None of them were willing to participate in any clinical trials. They all wanted the best therapy that their oncologists could give, but if one therapy had a 2% difference from another and if a question needed to be tested, my friends said they wanted that 2% difference even if the confidence interval was greater than 2%. I had difficulty explaining that.

I think all of the pediatric oncology groups have banded together, and virtually all children participate in a protocol. We do not see that with adult treatment groups. The advances have been far greater in pediatric oncology because of this consortium of professionals.

Dr. Buchman: Dr. Davis?

Dr. Davis: We have some great examples of patient participation in cystic fibrosis studies. Our center’s patients are actively engaged, and in any given year, one half of the patients with CF will volunteer to participate for clinical trials. Their involvement is critical, but involving that many patients requires that we educate them well. We have seen patient advocacy groups alter Food and Drug Administration (FDA) and other regulations. We can also address acquired immunodeficiency syndrome (AIDS) patients in that the FDA was willing to assign greater risk to AIDS patients participating in clinical trials because the risks of doing nothing were greater in these AIDS patients.

I would make one comment about the general population. As part of our Clinical and Translational Science Award, we have a significant clinic community engagement arm, and we also have a strong hypertension group that focuses particularly on hypertension in African-American groups and what medications that members of those groups will take first for hypertension. I was sure that when we asked the community, “What do you want us to study, based on the studies that have already been here?” they were going to say, “Let’s knock this hypertension problem.” Instead, they wanted to know why 14-year-old boys on a hot summer’s night will take a gun and shoot one another. We need to take hold of what the public wants to know in addition to what the academics want to know.

Dr. Buchman: A number of years ago, I was visiting a professor at the Karolinska Institute in Sweden, and the professor was collaborating with Astra Zeneca, which built a shell building and supplied some of the laboratory equipment at the institute. The institute also supplied equipment and most of the investigators, and there were also a few drug company employees working side-by-side with their academic counterparts. The investigators worked together, sharing resources and the like and, I assume, intellectual property rights in the end. The investiga-
Dr. Buchman: The academic issues of doing multicenter clinical trials are extraordinarily burdensome. Obviously, industry sponsors conduct a lot of multicenter clinical trials, but when a trial is sponsored by a university, that university has to approve everybody else’s consent forms, which may be different because the organizations have different ways of saying the same thing. These differences make an academic-initiated clinical trial virtually impossible to undertake.

Dr. Davis: A nightmare.

Dr. Buchman: Dr. Schulman?

Dr. Schulman: We established the framework to protect human subjects, and I would argue that we do not do that anymore. I would rather have a group of people that we pay to spend 6 months overseeing the trial than have 800 disparate groups spend 2 minutes on paperwork and check the box, which is what we have right now. The system is not benefiting the patients as much as we intended.

We do not have a central place where we can go to discuss these issues. Our institutions do not provide a forum. Industry does not offer such a place. The government does not have a place. The Office for Human Research Protections (OHRP) and the compliance offices of the Office of the Inspector General are not incredibly accessible. We put well-intentioned people who are doing good work in frightening positions when we suggest these government agencies. But we do not have a place to bring these well-intentioned people together to say, “We need to re-evaluate.” We need to ask if we can more effectively manage the people being coerced into trials. The fraud that is occurring rampantly in some of these trials, in terms of making decisions for our health system, then Merck could accommodate and make different choices.

Padma Natarajan (Infectious Disease Society of America): I am from the Infectious Disease Society of America. I lead our research committee, which is composed of infectious-disease investigators across the United States, and we too have been considering 2 issues: first, the recruitment and retention of physician scientists, and second, the major issues in clinical research. We are publishing papers on both issues. From the regulatory burden perspective, I have heard a lot of broad solutions today regarding our need to change the infrastructure of clinical research and to improve the IRB process, both of which are major steps. Can you suggest any smaller steps that we can take to improve the entire process? I have only heard broad solutions, which are very difficult undertakings.

Dr. Buchman: Why don’t we start with Dr. Gertz and run down the line.

Dr. Gertz: I would suggest that we need to educate the public on the importance of their participation in the clinical research process; if we could get more participants into the clinical trials, some of these issues related to moving research offshore would be reduced. By sharing the knowledge and having the public participate, we would produce better medical consumers who understand the process.

Dr. Buchman: Dr. Lipman?

Dr. Lipman: I wish I had an answer. I do not. I think the problem is us. The increased regulatory burden has been imposed because of the conflict of interests, the biases, the fraud, and all the other ethical lapses. Unless we can prove that our house is in order, the paperwork burden, the signatures, and the other regulatory issues will not go away.

Dr. Buchman: Dr. Davis?

Dr. Davis: Our CTSA is trying to streamline the research process from idea to enrollment. Most of us focus on the IRBs, a few people have suggested contracting, and we have heard Jeff Drazen’s suggestion that a uniform contract would help.

I sit in on the CTSA conference calls with our principal investigators, and I’ve noticed during these calls that each of these groups has its own bottlenecks, many of which involve IRBs or contracting, but some of which have too much paperwork and some have challenging bureaucracies or other issues, such as radioactive concerns or infectious disease concerns. Each institution has a responsibility to identify and deal with that institution’s issues.

We must also ask if we can tolerate consolidation of review processes in IRBs and if institutions will accept such changes. That is a bigger issue. For example, we have the Western IRB and consolidated cancer IRBs. Will these be accepted across the board? Institutional review boards were designed to be independent entities and to protect the patients, and IRBs take that responsibility very seriously.

Dr. Buchman: The academic issues of doing multicenter clinical trials are extraordinarily burdensome. Obviously, industry sponsors conduct a lot of multicenter clinical trials, but when a trial is sponsored by a university, that university has to approve everybody else’s consent forms, which may be different because the organizations have different ways of saying the same thing. These differences make an academic-initiated clinical trial virtually impossible to undertake.

Dr. Davis: A nightmare.

Dr. Buchman: Dr. Schulman?

Dr. Schulman: We established the framework to protect human subjects, and I would argue that we do not do that anymore. I would rather have a group of people that we pay to spend 6 months overseeing the trial than have 800 disparate groups spend 2 minutes on paperwork and check the box, which is what we have right now. The system is not benefiting the patients as much as we intended.

We do not have a central place where we can go to discuss these issues. Our institutions do not provide a forum. Industry does not offer such a place. The government does not have a place. The Office for Human Research Protections (OHRP) and the compliance offices of the Office of the Inspector General are not incredibly accessible. We put well-intentioned people who are doing good work in frightening positions when we suggest these government agencies. But we do not have a place to bring these well-intentioned people together to say, “We need to re-evaluate.” We need to ask if we can more effectively manage the risks that we have now in clinical research.

Finally, within the discipline of Infectious Diseases, we have a separate set of issues. Antibiotics are one of the most expensive drugs to develop (which makes no sense), and bringing a new antibiotic to market is one of the most expensive actions. If we succeed in developing a new antibiotic, we then want to wait until the current antibiotic has resistance. So the business model for antibiotics is skewed.

P. Natarajan: I was looking more for clarity and asking you to also suggest how we can use Capitol Hill. Some people recommend that we increase funding for the OHRP to hire more staff to review IRBs so we can reduce our timeline....

Dr. Schulman: However, the OHRP does not set reviews; they set up rules.

P. Natarajan: I’m sorry; I worded it improperly. But the OHRP does need more funding. That’s one thing that we can do....

Dr. Schulman: I received a letter once from the OHRP regarding a study. The study was anonymous and had nothing to do with patients. The study concluded that we needed to visit the OHRP’s website daily because the organization was not responsible for any previous written communication; the latest opinions are on the website. If I am risk averse and I am being told this by the OHRP, I am going to comply and not get in trouble.

To a trustee of Duke University Health System, what role does research play? Research loses money and potentially names the system in a negative story on the front page of The New York Times. The system is at risk for having Medicare payments shut down or huge fines or criminal prosecutions. If I were a trustee, I would recommend that we not do clinical research with our patients at Duke. So we need to change that framework if we are going to succeed at clinical research.

Dr. Buchman: One problem is that people who never see patients make the rules. Another problem is our IRBs. Every university should fire their IRBs, and we should have one, perhaps run by the FDA or under Health and Human Services, that everybody has to pay to review studies. Then, we have one IRB that Peruises the same consent for every institution.
P. Natarajan: That's actually one of our recommendations in a lighter form.

Dr. Buchman: This illustrates the issue. We know we have a problem. We do not know yet how to solve that problem. But the purpose of this meeting is to make people aware of the problem, because the first step in solving a problem is recognizing that it exists. A lot of people do not recognize that we have a problem here and that we are experiencing a crisis.

P. Natarajan: We do frequently address our representatives on Capitol Hill. Our physicians go to Washington, DC, to represent our organization and to present the issues that we identify in these meetings and that our physicians identify. Therefore, we provide subject-matter expertise on Capitol Hill to convince our government representatives. We have healthy relationships with senators and congressmen. Therefore, I make this point: we need to make these changes. We have recognized the problems, and the issues are better recognized during these meetings, but what can we do move forward?

Dr. Buchman: Let me identify another problem that we face. When representatives from the American Gastroenterological Association meet with the 21-year-old health care administrator for a Senator Durban who asks to which medical school he should apply and then representatives from the American Heart Association go to visit the senator’s office and from the Easter Seal Society go to visit, and representatives from these organizations each say something slightly different, the senator and staff laugh when the representatives leave. The senator and staff are saying, “When those people can get together and create a single plan, then maybe we will enact a plan to address these requests.”

P. Natarajan: We try to accomplish this unity.

Dr. Buchman: We’re too fractioned.

Dr. Davis: This happens when the doubling occurred. Everybody worked together and put aside their own specific requests. Industry joined us because industry said we needed action. Roy Vagelos from Merck advocated for us. Even the technological industries joined us and said, “We need to do this for the sake of the American public and for the sake of American industry.”

You said something else that I want to respond to: that you send your physicians to Capitol Hill. I think we should send our patients.

P. Natarajan: We do that too.

Dr. Davis: You know, we are seen by many as self-serving, as having our own best interest at heart. Now that I am a dean, my struggles are even worse. I want to keep our indirect costs high? Do not tell me that. The patients, however, are another matter, and some of our patients are pretty sophisticated. We heard from Mrs. Miller and Ms. Drescher, who, like many of our patients, understand how much research prolongs lives and improves their quality of life. They do not have to talk about the details. Your lobbyists or the physicians can address the details about the research, but the patient must step up and say, “If not for medical research, I would not be alive,” or “But for medical research, my child would not be alive.” We need those patients. Take them to Capitol Hill.