The Crisis in Clinical Research: Panel Discussion III

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Key Words: clinical research

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

Dr. Timothy Lipman (Washington, DC, Veterans Affairs Medical Center/Georgetown University Medical Center): Perhaps lunch has had a mellowing effect, but I get a sense of disconnect between this morning’s and this afternoon’s talks. This morning, we heard about a major crisis: nothing is getting done and we are losing our clinical researchers to old age, death, and senility. This afternoon, everything is going well primarily because the government is accomplishing a lot. I am a little cynical, but part of my role is to be a curmudgeon. Could we address this disparity?

Dr. Buchman: These issues are our concerns, although we have seen improvements in funding, for example, and in some priorities for clinical investigation. We have to look at the Clinical and Translational Science Awards (CTSAs) program, which is replacing some General Clinical Research Centers. We have looked at a CTA program whose initial sites were funded fully. Since then, those sites were funded at less than 50%. We looked at an educational program that improved but is still not sufficient to train clinical investigators for the present, notwithstanding the future. We have looked at the National Institutes of Health (NIH) budget, which has increased but can often be viewed as a sine wave. With this evidence of crisis in clinical research, how do we encourage people to go into clinical research and retain them if they do not know if there will be future funding, or which end of the sine wave is going to up for them? The risk is a bit like retiring today; we do not know which way the stock market is going to go.

Each of these represented agencies is doing great things and yet admits you can improve. Where do you see the problems? And regarding the success of your agencies, where do you stand and what do you need?

Dr. Anthony Hayward (National Center for Research Resources, National Institutes of Health): We do see things that we would like to accomplish. Above all, we would like to speed clinical trials and thus speed the progress of medical research. To do that, we need to work together. We need to develop a funding strategy that promotes cooperation and the rising of the best ideas to the surface so that we pursue those ideas. We need also to help people cross the so-called valley of death that Larry addressed after he addressed the Veterans Affairs on its virtual electronic record and other medical research priorities. That does not mean fundamental changes. I agree wholeheartedly with several of the other speakers.

Dr. Buchman: Dr. Throckmorton?

Dr. Douglas Throckmorton (U.S. Food and Drug Administration): The status quo is not acceptable, so we do need to make fundamental changes. I agree wholeheartedly with several of the other speakers.

Dr. Buchman: Dr. Kretsch?

Dr. Molly Kretsch (U.S. Department of Agriculture): Things are not well in the Department of Agriculture, at least in the Agriculture Research Service, where the clinical research is primarily done. We have many of the same problems that these other organizations experience, and our budget has remained flat for more than 10 years. Our scientists are reaching retirement age, and we are concerned that appropriately trained people will be available to fill those positions and that we will be able to attract them. We are in a serious state of uncertainty in whether we will be able to move forward with the clinical research that we need on the prevention side to show the role of nutrition and physical activity and to prevent disease.

Dr. Buchman: Ms. Embrey?

Ellen Embrey (Department of Defense): The biggest challenge for the Department of Defense (DOD) is the number of individuals who are choosing science in the biomedical arena in American schools. They are not going into clinical sciences; they are pursuing other areas, so we must concern ourselves with generating enthusiasm for these careers and then recruiting young people into our system. We are also prioritizing work to maintaining an infrastructure that embraces research because we are requirement driven. We are creating that environment now, but the DOD may not be able to sustain that level of funding. This year, the President doubled our advanced development research dollars when he addressed the Veterans Affairs on its virtual electronic record and other medical research priorities. That does not mean the DOD does not have problems; we got lucky this year.

Dr. Buchman: Dr. Tabak?

Dr. Lawrence Tabak (National Institute of Dental and Craniofacial Surgery): I resonate the comments made by the other panelists. Society needs to choose whether or not our citizens will make the investments required to sustain the efforts as represented by the members of this panel because all of these organizations are important. As we go forward, we hope society is willing to invest. We can just consider the title of this conference: “The Current Crisis in Clinical Research.” If that idea does not scare potential clinical researchers, nothing will. Therefore, if we can more regularly sustain the enterprise and if we can make the fundamental changes that our educational systems need, then we have a chance to enhance our infrastructure and our research and thus move forward.

Dr. Buchman: In my reasons for selecting panel members, I wanted to invite a representative from each of the primary federal agencies (with the exception of the CDC) because of
space) involved with clinical research. How do you see the communication between agencies? Could this meeting stimulate enhanced communication?

The surgeon general had actually planned to attend this meeting, but his acting health secretary had a conflict arise. But he provided an example of poor interagency communication: pediatric obesity, which is a focus of various funding agencies, but efforts are not coordinated.

The NIH has RFAs for pediatric-obesity research. The USDA is concerned about pediatric obesity, and the DOD is concerned because we do not want obese soldiers running around the battlefield, although soldiers are slightly above pediatric age. The Food and Drug Administration (FDA) also has a role because it approves therapies, devices, and medications to treat pediatric obesity. Obesity is a prevalent theme in the CTSA as well. How can the various agencies cooperate so that we can eliminate overlap in funding and research but also eliminate any gaps?

Dr. Tabak: Obviously, our interagency communications can be enhanced, although I must say I have seen enhanced communications over the past several years. I identify communication and collaboration that NIH has with each of the groups that are represented here.

Communication is about people. We like to talk about the nameless, faceless agencies, but success is about people. Our program staff are in the “trenches” and have the curiosity, the interest, and the intellectual stamina to reach beyond the confines of their office agency and make important connections. We cannot underestimate their relationships with others in the field. For example, we are accomplishing an important tissue-engineering project that the DOD sponsors with some modest cofunding from the NIH, which came about because of personal contact at a meeting like this. Organizations such as the American Federation for Medical Research can play catalytic roles because people and communication make things happen. We cannot minimize that.

Dr. Buchman: Ms. Embrey?

Ellen Embrey: America’s health system is really a series of systems that are connected in some places and unconnected in others. If we want to transform how we conduct clinical research, we must organize to make optimal connections between engineers, clinicians, and research scientists.

For the federal agencies to engage with each other, we must organize so that from the big-policy perspective and to define standards for data collection and ways to enable the different components, systems of systems can share information to improve their abilities to share knowledge. We could all benefit from knowledge management in its purest sense. We just need a framework in which to build an effective knowledge management system.

We have opportunities. We are all driven by congressional oversight committees who have very clear guidelines. The president has provided clear guidelines about what he wants to see. We need more forums in which to build visions for how we will work these issues together and to establish relationships between different priorities—but important connections between those priorities—to move forward.

Dr. Buchman: Dr. Kretsch?

Dr. Kretsch: This symposium has been good. Anything that we can do to enhance communication is important. Speaking from the perspective of the USDA ARS, anything that we can do to make others aware that we conduct clinical research is important because the public is not aware that the Department of Agriculture is doing clinical research on human nutrition. The public tends to associate the USDA with the agricultural side rather than the food side. This has been an important conference, and I am glad I could participate.

Dr. Buchman: Dr. Throckmorton?

Dr. Douglas Throckmorton: I agree that success lies in the people. That has been my experience in this sphere. People get interested in a topic and they start talking with the National Cancer Institute and they end up with an Interagency Oncology Task Force, for example. Communication is personalized and is also a priority setting. My agency is resource-challenged, so communicating and interacting takes hours that otherwise would go toward our objectives.

I like what Dr. Kretsch said. Role understanding is very important. I attend many meetings at which people do not understand what the various agencies have to offer or what roles the various agencies play. Then, they are disappointed when they work through a project only to find that other people from other agencies need to participate or could have added to the resources. So, understanding is also an important part, and meetings like this facilitate understanding.

Dr. Hayward: To be efficient, we need to maximize and share the resources we have. The world of communication is changing so much. We do not support Twitter or Facebook; we do not network the way younger people do, and they believe those networks are essential to make life work.

Therefore, we are going to meet with our CTSAs and determine our priorities, which include cataloging the research resources that are available and connecting scientists so that they know about these resources.

So to succeed, we involve people from, for example, the FDA, and we put them on our committees to know what they know. People at the CDC, for example, have been effective in hosting conferences with us on prevention research. There is movement in partnering, but communication is a major challenge that we face.

Dr. Buchman: Dr. McPhaul?

Dr. Michael McPhaul (University of Texas Southwestern Medical Center): I am at UT Southwestern and I’m associated with the CTSAs there. From the very outset, I have really appreciated the concept. Having a number of isolated components and programs that do not cross-pollinate made a lot of sense to me.

I did want to comment on the CTSAs over the last 2 years and how that relates to how things are going counter to the instructions that people received to formulate their CTSAs. Frequently, when people came to program officers and asked them for direction, the program officers answered, “You come up with the best solution you can and if you are competitive, we will fund you and you will go off and you will make your own solution to the overall problem.”

In the last year and a half, I have seen an edge to some of the actual components of administering the program. I say this not as a principal investigator but as an observer. Some of the processes seem to run counter to that spirit, and I wonder whether some of you can speak to this. I am speaking of minimal processes like budgeting, carry forward, procedures about supporting students or fellows 100%, whereas before, we could supplement or mix funds. These things do not help productivity. The actual material effect I can speak to first hand is to decrease the number of people who are engaged in CTSAs-related training programs. I suggest this because the issue seems to be a symptom of a process that has a good heart but, independent of funding, the process ossifies, centering on directions or procedures that do not add value.

Dr. Buchman: Dr. Hayward?

Dr. Hayward: Consumer input is tremendously helpful to us. We have made changes to the program in the last few years, like...
allowing postdoctoral fellowships under T awards and allowing research overseas. Some rules, such as limits on using multiple funding sources, are in place because of the idea that if the government buys 75% of someone’s time, then that individual tells his department chairman, “I am not going to go do that clinic because my time has already been sold.”

In real life, that individual may not work in an environment in which he is threatened for time, but the rules that are good for some places may not be good for other places. All I can promise you is a continuing active review of these issues. We are certainly continuing to review these rules, and we are aware of the concerns in the community. Otherwise, as far as carryover is concerned, the question may be adjusting to the rules and how to make them work for you.

Dr. Buchman: I have another global question. We have heard that the number of academic faculty is decreasing and that the average age for R01 funding—and perhaps funding from other agencies—is increasing for first grants. We have MDs, very few of whom are getting funded, and the majority of MDs who are funded are doing basic research. How do we attract people to clinical research, train them appropriately, and retain them in clinical research?

Dr. Tabak: First, we need to make the enterprise attractive and, unless we find sustained support, at all levels, clinical research just is not an attractive career path. Let us assume that you are fortunate and you do attract a good young person into the career path. Then mentorship becomes crucial. We collectively have become skilled at many things, but we still need help with teaching people to be great mentors. Mentors are born—I am not sure if you can make them, but if somebody wants to disagree with me, tell me the secrets and I will write them down. Often we see young people, because of mentorship—perhaps well intended but not optimal—go off into cul-de-sacs, become frustrated, and drop out of the system.

Physician scientists or general clinician scientists do not fare quite as well in their clinical research effort because they give up. They do not submit that amended application to obtain the success rate that is greater than that under the initial submission. They give up for many reasons, such as the pressures to do the addition clinics. I’m not saying that someone is wrong to drop out, because that person may have good reasons to leave. However, senior leadership—the mentors—need to recognize these issues and create an environment that allows this young person to try again, because often, persistence does win. Elias Zerhouni used to say that persistence should win over brilliance. Honestly, I am an example of that. Don’t think you need a referee here.

We need a sustained enterprise, and we need strong mentors: 2 components that we really have to continue to pursue.

Dr. Buchman: Let me ask you a brief follow-up. Why do you think that MDs who apply for funding have a lower funding level, and why do MDs who do clinical research appear to have the lowest funding of all investigators? Is that because of poor mentorship? Is that because the basic scientists who review grant applications do not understand the complexities of clinical research and that not every variable can be controlled, as in a rat model? Do we need to refine the peer review process so clinicians are reviewing clinicians’ applications? What is the problem and what is the solution?

Dr. Tabak: I do not have one answer to that complex question. Data show that the lower success rates among physician scientists performing clinical research relate to the fact that the scientists do not submit amended applications with the same frequency as their basic science colleagues. One of the unusual features of the NIH system is that amended applications tend to fare better, but that is a fundamental rule of grantsmanship. If you do not submit or, in this case, resubmit, you will not get funded.

Again, these physician scientists may fail to resubmit for a number of valid reasons, such as pressure for time or other opportunities. I am not trying to be judgmental, but at the local level, mentors need to analyze those trends and factors and work to incentivize these young people to try again, because we are losing tremendous opportunities.

We have just gone through an 18-month process to enhance peer review, and many of the proposed enhancements will impact clinical research by focusing attention on the larger issues—on the impact of the potential findings and less on the details for basic research and to buffer concentrations for clinical research, which is going to help science in general. By allowing potential study section members to extend their service over a longer time, we will help clinician scientists who cannot travel to Bethesda 3 times a year.

Dr. Buchman: Back to the issue of how to attract, educate, and retain those in clinical investigation: from a DOD perspective, are there incentives? Do people get into the DOD because they want to spend extra time? Tell us about your extramural funding, how attractive that is to those who want to engage in clinical research, and how that might be enhanced?

Ellen Embrey: We have different models within the DOD. The army, navy, and air force have both intramural and extramural programs for clinical research. The funding is designed around their focus for how they address specific occupational risks to their population. The air force looks at sleep deprivation and oxygen-deprived environments. The navy looks at undersea issues and exposure to different nuclear particulars to answer their particular health questions. They engage in both intramural and extramural competitive programs.

Because we are a system—a relatively closed system—each of the services can build career paths that allow clinicians to move in and out of research laboratories and then go back into practice if they so choose. Those paths offer opportunities that few systems have, so we can attract people who want to make a difference, and we give them opportunity, as they mature and gain skills, to move anywhere in the world.

Our issues come with finding the qualified individuals. Our biggest challenge is incentivizing them to join the military during war time with the threat of deployment. However, we are satisfied with our system.

Dr. Buchman: Dr. Kretsch, is it more than money?

Dr. Kretsch: The issue is more than money. We have 2 kinds of clinical researchers in the USDA: we have PhDs who are trained in human nutrition clinical research, and we have MD/PhDs who also conduct research. These researchers are primarily at our locations and are associated with medical schools.

One of the advantages we have had—but this advantage has eroded because of funding—is that we have been able to provide our researchers with a salary or a portion of their salary and some contributions toward research cost. When you do not spend a large amount of your time writing grants, the salary and research funding is a real incentive. Unfortunately, this incentive is eroding because of the flat funding.

Now, increasingly, our researchers—whether PhDs or MD/PhDs—are spending more time trying to attract funds from other sources, in addition to the base funds that they receive. The base funds, however, are still an attraction for scientists coming to the USDA.

Dr. Buchman: Dr. Throckmorton, aside from the orphan drug program, which has a difficult time developing anything with only $15 million a year. I am amazed that your researchers do as much as they do, and certainly, when the FDA approves an orphan
drug, everybody is excited. What do you see the agency doing in creating incentives for drug development when less than 200,000 people in the United States have a given orphan disease? With regard to not only orphan disease, but all diseases, where do you see the agency fitting in the education process to have more clinical investigators, both within and outside the agency, so that you have qualified staff to do the things that the agency is empowered to do, in addition to assisting the agency with review and other uses?

Dr. Throckmorton: We are a net consumer of those trained physicians, but when people are interested, they come to work for us, and we see if we can turn them into regulators. We do look to MDs to fill that niche. We do conduct intramural research, but that research is quite targeted: we need to know whether candy contains too much lead or whether a drug in postmarketing setting is associated with some adverse event. We do not participate in free-ranging questioning but rather a response to need, and much of it to a regulatory need, such as to write a guidance that says, “To develop this drug, you need to follow these rules.”

For us, providing that clarity is an important part of making a difference in efficient product development. Clarity reduces risk if a drug manufacturer must decide whether to invest in a new antibiotic. They want to know the rules that they must follow to get that drug approved, and the more ambiguous the rules are, the worse off the drug manufacturers are. To create that clarity, we need intelligent people who can think in that regulatory frame and ask not the basic science question but a different kind of question: of scientific policy development. We do not have the infrastructure in the United States to develop those kinds of people; we find a handful in academic institutions that discuss drug development and regulation in an unusual way. Pharmacy schools do the best job of talking about scientific policy. We would like to build a better cadre of regulators, but that is one of many infrastructure pieces that are missing.

Dr. Buchman: How do you see the process evolving to have earlier discussions and earlier involvement between the agency and either academics, where devices are often developed and some medications are developed in the early stages, or industry? How can you prevent a lack of communication that results in someone coming to you with a device or a medication at a later stage of development and then everyone pointing fingers as to whose fault it is when things do not proceed? How do you see moving that process earlier?

Dr. Throckmorton: I have spent time talking to manufacturers to try to understand their world because they have economic concerns that I would not understand and that will drive them to decide when to come to us. That time equates to the personal connection issue. So the senior leadership at the Center for Drug Evaluation and Research talks to Merck and the manufacturing sector and say, “We really are open for business here. We’re happy to talk to you. We are prepared to change.” This is not a closed system. We do not enjoy those conversations, and we must mean what we say to the manufacturers, get them to believe us and bring in that new antibiotic earlier than they would otherwise, and we can then converse about the process of getting that drug on the market. We need to give the drug manufacturers and the FDA a chance to discuss more efficient ways to develop and market drugs, which used to take 10 years and too many thousands of patients. How to stimulate that discussion? I do not have a good answer beyond being willing and interested and conveying that to people.

Dr. Buchman: Dr. Hayward, how do you address the concerns that CTSAs are a great idea but they are not sufficiently funding the education of clinical investigators and we have related issues like the K-23s? In additions, there are salary limitations on loan repayment forgiveness, which the AFMR was largely responsible, that have not been indexed to inflation, and as tuition has increased, funding is no longer adequate loan. What are your thoughts on this?

Dr. Hayward: We will never have enough money for everyone, and clinical researchers are extraordinarily prepared to face, tolerate, and overcome extreme barriers. We are clearly a nation that incorporates an enormous number of highly talented people. I wonder if we do not run a medical education system that could work against us sometimes. We train physicians who come up with the right answer, and our examination system is programmed to produce people who always know the right answer. We never ask, “How would you do better?” The whole basis for wanting to do research is to figure out what we are doing wrong and how we can do that better. If we can create an environment in which that questioning spirit is treasured, we will do better.

Dr. Buchman: Thank you all very much. I hope our conversation here will serve as a stimulus, perhaps through the leaders as well as the press who have attended, so that the priority of clinical research can be advanced. Perhaps, in time, congressional hearings or a multiagency task force, for example, will identify the locations where we are conducting clinical research, who is paying for the research, and what current funding actually is. We will struggle to fully envision where we need to go if we do not know where we are.

We have accomplished something unique here by gathering people who have never met before. We can start and enhance communication even just within this room, certainly within the government and perhaps between academia, industry, and government as well. Industry clearly needs to be included in the equation as well. Hopefully, the press can get the word out to the American people, who are the ultimate consumer of the results of our efforts and mis-steps.