JOURNAL OF CLINICAL RESEARCH BEST PRACTICES

Vol. 3, No. 9, September 2007 "Can You Handle the Truth?"

Greg Koski on Human Subjects Protection

By Norman M. Goldfarb

Greg Koski received his A.B, Ph.D. and M.D. degrees at Harvard University and has maintained an anesthesiology practice at the Massachusetts General Hospital (MGH) since 1984. He has also served as Chairman of the Massachusetts General Hospital Institutional Review Board, Director of Human Research Affairs at Partners Healthcare System, Director of Henry K. Beecher Memorial Research Laboratories, and was the first director of the Office of Human Research Protections (OHRP) at the Department of Health and Human Services.

How did you get started in medicine and clinical research?

From the time I was a little kid, I wanted to be a physician-scientist. I know little kids aren't supposed to know what physician-scientists are, but I had a fascination with science and I really wanted to see it put to good use for people.

When I was in seventh grade, my grandmother came down with a brain tumor. She underwent investigational radiation therapy and it was pretty impressive. They told her there was nothing they could do for her, but she actually got better long enough at least to say goodbye to all of her friends. The experimental treatment had made a big difference in her life and our family. That's when I decided to go to medical school and put science to work for people.

I got my Ph.D. in physiology and then went back to medical school and ultimately chose anesthesia and intensive care. I love the physiology and the pharmacology. I alternated between doing clinical work and doing basic science for two-year stints. There's a natural parallel there between anesthesia and clinical research. In anesthesia, there is a very real and necessary relationship of trust between the doctor and the patient. Once you receive that anesthetic, your life depends upon someone who is going to, above all other considerations, take care of you. That is exactly what an investigator ought to be doing for somebody in a clinical trial.

As a young faculty member at the MGH, I was asked to serve on the IRB. Early on, I was horrified by a situation I found myself in. I was given a protocol from my own department to review. It was just disastrous. It was a real eye-opener. I complained loudly enough that I was put in charge of trying to make things better. That's how I ended up becoming chair of the IRB and then Director of Human Research Affairs.

In the wake of problems that were going on in clinical research at the time, the Office of the Inspector General decided to conduct a study of the whole IRB process. They assigned the project to their office just down the street from the Mass General. I got a call one day from Mark Yessian, who authored all of the OIG reports. He said, "I'm from the Office of the Inspector General. Can I come talk to you about human subjects protection?" It scared me to death. As it turned out, he was impressed with the innovative things we were doing at the Mass General, for example, the notion of greater flexibility, but with more accountability and the notion of shared goals and shared responsibilities. These approaches became the philosophical foundation of our work in Washington in the early days of OHRP.

What were your goals at the OHRP?

At the time, the so-called twin pillars of protection of human subjects were considered to be IRB review and informed consent. At the Mass General, we felt that that this approach took away from the investigator and other members of the clinical research team their responsibilities for protection of human subjects. The IRB is not the primary protector of human subjects in research; this is a responsibility shared by everyone involved in the research. Of course, much of this responsibility falls heavily on the investigator. If researchers were properly trained and motivated to take on these responsibilities, rather than having a confrontation between investigators and IRBs, we would have a much more collaborative, effective and productive system. That was the culture that we worked to build at the Mass General, and that's what we set out to accomplish at OHRP.

I never believed that more regulation was the way to go. A "culture of compliance" was not what we wanted. We wanted to build a "culture of conscience" where people didn't do the right thing because it was required by the law, but because of their own sense of moral responsibility and personal integrity – because it was the right thing to do. We emphasized proactive approaches to prevent injury, rather than reactive approaches that would punish someone when something bad happened. Obviously, the goal was, and is, to prevent harm, not to react after harm occurs.

It was very clear from inspections done by the predecessor office, the Office of Protection from Research Risks, that institutions simply weren't meeting their legally binding promises (assurances) to develop and maintain effective systems for protection of human subjects. In many cases, massive amounts of work were being thrust upon a few individuals who were well-meaning but not capable of dealing with the loads. The OPRR found that more than half of the top twenty institutions across the country had severe systemic deficiencies. Those were the ones that ought to have been doing the best, so you can only imagine what it was like at the others.

The OPRR inspections found deficiencies in meeting operational requirements set forth in the regulations. But when you have operational deficiencies, it raises questions about whether there are deeper problems. For example, are IRB members properly trained and qualified? It turned out that there were no requirements for training of IRB members or chairs or managers. There were no standards. There was almost nothing. What the government had done was to create a process that, by and large, was going through the motions without any real evidence that, in fact, it was doing much good.

We still don't have direct evidence that the current process is actually preventing harm. We need solid empirical research on whether the IRB process is actually working. That means not just being in compliance with the operational regulatory requirements, but having a process that is able to identify a real risk to subjects and able to change things to achieve a higher degree of protection. Most of us want to believe that is the case. In many instances it probably is, but we really need better evidence that the whole process works.

The TeGenero study is a contemporary example of failure across the entire spectrum of the clinical research team from the sponsor to the competent authority (as they call the regulatory agencies in Europe), to the IRB, to the investigator, to the CRO, to the informed consent process. It was a complete and total failure. After everything that has gone on and all of the energies that have been invested in this process, how is it possible that one can have multiple sequential failures that would allow six young men to almost be killed? It underscores that although we may have made progress, we still are a long way from where we need to be. That protocol was improperly and unethically designed from the outset and no one caught that. No one spoke up and did anything about it. It's just unconscionable. Because the well-being of the subject is our highest priority in clinical research, every

member of the team must be willing and empowered to speak-up and take action when necessary. We must continue to work toward that goal.

What advice would you give to the head of research at a medical center interested in building a "culture of conscience"?

First of all, the commitment has to start from the top. The people at the top have to acknowledge that research is a critical part of our mission and that people are counting on us to do it right. The subjects' safety and well-being has to be our first consideration; anybody who doesn't want to look at it that way should go find another place to work. The approach is simple, really. But this commitment from the top has to be backed-up with proper actions and resourcing of the process, a continuous quality improvement program and proper training of the entire research team.

What is the research sponsor's role?

I don't know of a single research sponsor that would ever want to harm a research participant, but it's still a question of priorities. Industry knows that it is in its interest to pay for an effective IRB review. It didn't used to. Now it realizes that if you don't get a good IRB review, you are potentially going to be in deep weeds, and a subject may be in the hospital while the sponsor ends up in court and the stockholders abandon ship.

Similarly, industry needs to wake up and acknowledge that it is not in its interest to have research being done by untrained, unqualified personnel. That goes across the board from the investigators on down. Allowing people to become investigators with no training, with no demonstrated qualifications, even in areas outside their area of clinical expertise, is just mindless. How can we possibly justify that? Industry is now beginning to see this. It has the power to change the situation overnight by simply stating that in five years it will not place a study with an uncertified investigator. And FDA could help us move in that direction by subjecting non-certified investigators to greater scrutiny.

The public is becoming better informed about clinical research. Soon, people are going to say, "Wait a minute, you mean we have investigators who haven't been trained, who aren't certified?" Once the public begins to recognize the importance of having accredited human research protection programs and certified research personnel, we are really going to move forward.

What is happening with accreditation programs?

From the time that I went to Washington in 2000, the Department of Health and Human Services began to speak strongly in favor of accreditation of human research protection programs. We use third-party validators in education, in medicine, in animal research. There is no reason why it shouldn't work in human research as well.

In South Africa, in New Zealand, in Canada, in countries in Europe, accreditation is emerging as the way to go. The World Health Organization has developed programs for surveying and evaluating the performance of ethics committees and implemented a form of accreditation, a recognition program for ethics committees that demonstrates through a rigorous peer review and site visit that they have achieved at least the operational standards in the WHO guidelines.

Clinical research is beginning to mature as a global enterprise. There is a long way to go, but we are taking steps in the right direction.

For a long time, most clinical research was done in academic centers, where there was a belief that people knew what they were doing. This country did not admit that Nuremburg had anything to do with us, but that was just denial. It wasn't until the mid to late '50s that we became aware of the fact that, yes, we did have our own ethical problems.

We've seen now the unfortunate cycle go around many times: first there is a problem and then a reaction. Then we go around the cycle again until there is another problem. We have never adequately tackled things in a comprehensive and proactive manner.

The death of Jesse Gelsinger was a tipping point. We had the commitment of President Clinton and the DHHS Secretary to create a new office, a commitment from all of the Federal agencies, a commitment from academia. All the forces were aligned towards making the system work once and for all.

It is tragic that in the last few years we lost that momentum. There has been far less emphasis by the current administration on protection of human subjects. Cutbacks in the OHRP budget have restricted its mission and effectiveness. As far as I can tell, the quality improvement program OHRP implemented in 2001-2002 has been effectively gutted. The integration of FDA and OHRP oversight of IRBs once ready to be implemented was abandoned. Without adequate funds and personnel for new programs, OHRP has once again begun to slip back from a prevention-focused, proactive approach to a more reactive, compliance-focused approach.

Fortunately, AAHRPP accreditation of human research protection programs is really taking hold now. There are hundreds of institutions in the queue for accreditation now, including some outside of the United States. AAHRPP accreditation should be something you work for; you don't get your college degree by taking a couple of courses over the Internet. We are better off maintaining high standards. Institutions that achieve accreditation can take pride in what they have achieved. Once programs have achieved initial accreditation, maintenance of accreditation is decidedly easier. As the former Director of OHRP, I can tell you that any institution with AAHRPP accreditation will never have its Federalwide Assurance suspended. You could never achieve AAHRPP accreditation with that level of deficiency.

Like any other profession, clinical research should be setting standards for itself; it should be policing itself. If we can continue to move down that road, we move away from the emphasis on compliance and towards conscience, integrity and responsible conduct; this is the professional approach.

If OHRP and FDA had the courage and foresight to come out and say that they are going to focus their compliance oversight activities on unaccredited human research protection programs and uncertified research personnel, which is fully justified, we would see a dramatic acceleration toward accreditation. Similarly, if industry were to take a strong stance with respect to accreditation, as well as certification of investigators, we would see a similar dramatic shift from a compliance-focused paradigm to a professional paradigm.

If we are not able to achieve change driven by industry, by government, and research professionals themselves, then the public getting smart enough to just say "no" would be a very powerful way to leverage change. As we all know, the willingness of people to participate in trials is the limiting factor in the entire clinical trials process.

What are the prospects for human subjects protection overseas?

My dream is to bring together committed individuals and institutions from academia, industry, government, ethics, the whole profession, to develop global standards for certification of professionals, for accreditation of sites, for accreditation of human research protection programs. Everyone could help pay for it. We can have a global network of

research sites operating with fully trained personnel under the auspices of accrediting agencies.

This is akin to building a system like the National Air Transportation Safety System. To have airplanes take off in New York and land safely in Bangkok, we depend upon a system with standard protocols to transfer an aircraft from the time of take-off to another control center as it crosses the country, and crosses the ocean. We can fly planes safely around the world because we have such a system in place. If we didn't, nobody would fly because planes would be crashing into each other all the time. The air transportation industry is more than happy to help pay for the system because it is in their interest to do so. That is where we need to go with clinical research.

The World Health Organization has been working toward this goal for ethics committees for about a decade now. This effort is known as SIDCER, the Strategic Initiative for Developing Capacity for Ethical Review. WHO has established forums of ethics committees in five regions of the world. It has created standard operating procedures for ethics committees. It has created standard procedures for surveying and evaluating performance. It has created a recognition program. If we are able to extend this network to investigators and coordinators and sites around the world, we could have the robust research network I am talking about. It could be paid for by a trust funded by grants from private foundations and funds from industry and governments, all of whom would be users of the system. That is the dream that I continue to work on pretty much every day.

ICH GCP has now been adopted by over 130 countries around the world. Now we need to build systems to implement and support the guidelines. We are rapidly becoming a web-based world. We should be using the Internet to make the clinical research process more efficient and safer. We can do it, it just takes the commitment, and of course, the resources, but "if we build it, they will come."

Further expansion of clinical research in developing countries is going to be very rapid. Industry understands that if sponsors go into countries that don't have a clinical research infrastructure, their liabilities are huge. If a company is going to do clinical trials in Nigeria, for example, it is in the company's interest to have a team in Nigeria that is well trained, has good systems in place, and is fully accredited according to internationally accepted standards. It is beginning to happen in India, in China, in Eastern Europe and Latin America. Industry knows that these aren't just developing countries; they are emerging markets. In the United States, we're somewhat complacent. We could find ourselves at the rear of the wagon train if we don't continue to make progress in our own country.

We can learn from developing countries. Let me give you an example: I gave a talk about informed consent at the Pan African Bioethics Initiative meeting in Cape Town several years ago. After my lecture, a delightful gentleman in the native dress of his African village pointed out that, in his village, they don't call the process "informed consent" because those words imply that the expected outcome is consent. In their village, they call the process "informed decision-making" because they want a well-informed decision either way. I was humbled because here was someone who, with little formal training, taught me and everyone at that meeting an important lesson.

What are your thoughts on local vs. central IRBs?

Collaborative review is a much more effective and efficient way to operate. While I was at OHRP, we worked very hard with the National Cancer Institute to develop what they call a central IRB process but is actually a tandem review process where a central committee does the primary review. Participating sites can accept it or reject it. The primary review includes experts that would be difficult, if not impossible, for multiple sites to assemble. Some of the

NCI cooperative group studies have 800 participating institutions. Instead of having 800 IRBs and 800 sets of duplicate files and 800 consent forms, you have one primary review; you have one consent form.

Each site can then direct its resources towards local concerns. If it has unique requirements for the consent process, it can put them in. The local site is best-prepared to determine whether or not it has the personnel, the resources, the facilities to do a particular protocol. That's what they should be focusing on, not doing another redundant review of the protocol.

We need to get the "institution" out of institutional review boards. It may have been appropriate back in the '70s, but it is no longer appropriate today. Independence is what we need now. In the late '90s here at Mass General and Partner's Healthcare, we de-institutionalized the IRBs by combining members from the various hospitals in multiple IRBs so they weren't reflecting a single institutional view. If you take an institution like Rochester, or Duke, or Johns Hopkins that ran into big subject protection problems, where did they turn when they needed help? They turned to an independent, for-profit IRB to bail them out. For multi-center trials, it makes so much more sense to have a centralized review and then bring in the local expertise after that is done. However, it is not going to be a one-size-fits-all model. Some protocols have to be reviewed locally. Greater flexibility and greater accountability is a much better way to go.

Does your work on conflict of interest have any particular focus?

If we can't develop new products and bring them to market, then no one is going to benefit from them. So our processes in science and ethics need to be compatible with product development. But when you get into a situation where an individual has competing interests, we need to make sure that the interest of research participants and the integrity of the science are properly protected.

For example, we can look at financial disclosures to sponsors. Sponsors aren't required to make those disclosures to the FDA until they submit a new drug application. We need more openness up front. The disclosures should be made not only to the sponsor but also to a separate board, not the IRB, that looks at the conflicts. Greater openness is the answer for dealing with most conflicts, but disclosure alone is not enough. It needs to be disclosure with appropriate actions to ensure that the conflicts don't cause problems.

How do you balance your full time anesthesiology practice with all of this other work?

I am very passionate about the things that I do. I have wonderfully supportive colleagues and an absolutely wonderful wife, Linda, who has helped me and supported me in everything I've tried to do, even at her own personal sacrifice. I am very fortunate and grateful.

What are you passionate about now?

Fostering creation of a global network with global standards and professionalism within clinical research is my passion. I am honored to be affiliated with organizations like ACRP, APPI, the World Health Organization, IRBnet and others who are working towards these shared goals. I haven't run across another field where so many people are so passionate about what they do as in clinical research. Seeing the level of commitment they bring to what they are doing, the number of people who are willing to stand up and say, "I'm going to do this right or I'm not going to do it at all," gives me great hope for the future.

Interviewer

Norman M. Goldfarb is Managing Director of First Clinical Research LLC, a provider of clinical research best practices information, consulting and training services. Contact him at 1.650.465.0119 or ngoldfarb@firstclinical.com.