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Greg Koski on Rethinking Human Subjects Protection

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Greg Koski received his A.B, Ph.D. and M.D. degrees at Harvard University and has practiced cardiac anesthesia at the Massachusetts General Hospital (MGH) since 1984. He has also served as Chairman of the Massachusetts General Hospital Institutional Review Board and Director of Clinical Research Support and Development, 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 U.S. Department of Health and Human Services. He is past-president of the Academy of Physicians in Clinical Research and is the president and co-founder of the Alliance for Clinical Research Excellence and Safety, a non-profit organization building a global network for clinical research modeled after the international air transportation system.

When we talked in 2007,[1] you expressed concerns about our approach to human subjects protection. Has anything changed?

Yes and no. Training and education are more extensive than they were a decade ago, and so is awareness. We also now have well developed, although underutilized, processes for certification of clinical research professionals. We have evidence of considerably better compliance with the regulatory requirements at our institutions, and all of this is good. Unfortunately, however, we started down the wrong road 40 years ago and have never looked back until now, only to realize that we may have taken the wrong path. Today, we find ourselves with an inefficient, compliance-focused system for "protection of human subjects," an approach based on protectionism that places enormous burdens on the research process, with little evidence that it is actually doing any good to make research more ethical or safer. Even OHRP now recognizes the need to have a more effective and efficient approach — a message that is also heard clearly from both the research and ethics communities.

So, do you think it's just a matter of time before all the issues are addressed?

Unfortunately, no. We are still focused on a "culture of compliance," rather than meaningful ethical review. If we've proven anything since the Belmont Report, it's that adding and enforcing regulations simply does not work. In fact, it's counterproductive and misses the point. Our goals are to ensure that all research done with human subjects is ethical and responsibly done. We have failed in the latter by not adequately focusing our efforts on those who actually do the research and bear responsibility for ensuring the well being of the subjects, namely, the investigators.

As in the practice of medicine itself, in the world of clinical research, regulatory compliance consumes a huge amount of time, resources and energy, so much so that it has become an impediment to doing research. It takes many institutions months to start up a trial. There is still no direct evidence that the current process actually protects human subjects. We have built a system that is similar to the Transportation Safety Administration. We screen every research study and require prospective approval despite the fact that most, in fact very few, pose serious ethical or safety issues. Unless we believe that our scientists today are likely to repeat the atrocities of Nazi physicians or the abuses of Tuskegee, there has to be a better way. Our current approach is inefficient, ineffective and excessively compliance-focused.

The recent Advance Notice of Proposed Rulemaking (ANPRM), "Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay and Ambiguity for Investigators," is yet another example of how we continue to tweak a flawed system that is fundamentally based on assumptions that are no longer relevant. I reject the assumption that investigators are inherently "bad" and that human subjects need to be protected from them. Instead, we should be giving more responsibility and flexibility to investigators, sponsors and research teams and holding them accountable.

When we rely on the IRB as the primary protector of human subjects in research, we reduce the investigator's sense of responsibility. The existence of IRBs and all the rest of the regulatory compliance apparatus do not, in and of themselves, protect study subjects from harm or make a study ethical.

What is the alternative?

The answer is to extend the paradigm of professionalism that is used throughout medicine to the clinical research endeavor. Clinical research involving human subjects is a subspecialty of medical practice and should be treated as such. Physicians in clinical practice are credentialed and granted privileges based on their qualifications and experience. They are, of course, still subject to oversight and peer-review, but they bear primary responsibility for their actions. They lose their privileges if they fail to meet their responsibilities. Why should clinical researchers be any different? Being allowed to do research on human subjects is a privilege, and that privilege should be earned through rigorous training and objectively validated expertise, as in clinical practice.

As Henry Beecher stated so eloquently 40 years ago, if we really want to protect human subjects, we need to rely on well-qualified, well-intentioned and committed investigators (and other members of the study team), and we must hold them accountable.

People are tired of hearing me say that instead of the current culture of compliance, we need a "culture of conscience," so let's change the tune and call for a "paradigm of professionalism." Investigators should do the right thing not because the IRB says so, but because their own educated sense of moral responsibility tells them it's the right thing to do. Investigators need to better understand and fulfill their responsibilities. They need to conduct themselves as true professionals.

So, do we close all the IRBs?

Not at all. IRBs, more correctly called "research ethics committees," would still play an important role in oversight and peer review. But instead of focusing on regulatory and procedural compliance, IRBs in a professional paradigm would focus on important questions of safety and ethics. Institutions would use their existing professional credentialing processes to regularly review the qualifications of investigators as a condition of granting those qualified the privilege of engaging in research. The expectation should be that they will conduct their activities responsibly, and if not, they would lose their privileges. Under this paradigm, there is no need to prospectively review and approve every protocol. Of course, any protocol would be subject to review at any time, and certain types of high-risk protocols might still be subject to consultative review and disapproval, moving the default position from approving greater than 99% of protocols that were okay to begin with, as is now the case, to stopping the less than 1% that are problematic. Many details would have to be worked out, but we have a century of experience with this paradigm in the rest of medicine and there is no reason that it will not work for clinical research. Given the will, we will find the way.

It makes no sense to allow individuals to become clinical investigators with essentially no formal training or demonstrated qualifications. Imagine if we were to take such an approach with cardiac surgeons! Nevertheless, in clinical research we do it all the time. In the majority of industry-sponsored clinical trials today, the most rigorous training the investigator goes through is a one-hour start-up meeting with a company or CRO representative. Should we be surprised to find that nearly 40% of these trials have deficiencies that are directly attributable to the failure of investigators to meet their responsibilities?

What is the role of the study sponsor?

Like the rest of us, study sponsors share responsibility for ensuring the safety and well being of subjects in their research. At the end of the day, sponsors pay for studies to be done well. No one benefits when subjects suffer harm in a research study. Study sponsors could dramatically bring about change in our current approach by simply requiring that all investigators are properly trained and qualified before a study is placed with them. Sponsors can and should recognize and depend upon professional certification as a demonstration of an investigator's commitment and competency.

What happens to all the regulations?

The regulations would have to be adapted to the professional paradigm. Regulations and compliance with them would still play an important role in ensuring integrity of the process, and to ensure proper study conduct. The key difference is that the investigators would bear greater responsibility and would be properly trained to meet their responsibilities. There would still be an effective system of peer review and oversight, but much of the oversight could be directed toward ensuring quality and safety rather than just regulatory compliance.

The ANPRM includes some very good ideas, such as having a single system of oversight and uniform regulatory interpretations and requirements with risk-based review processes, but it also demonstrates why our current compliance-oriented system is failing. I will be surprised, after considering the thousands of often contradictory individual public comments, if the ANPRM leads to much, if any, substantive change. We no longer need incremental change — we need disruptive, transformational change. We should convene a new National Commission to chart a whole new path forward, starting with the assumption that research and investigators are good, that the public need not be "protected" from them as if research is an untrustworthy criminal activity, and move toward a professional paradigm. We could easily use federally funded demonstration projects as a mechanism for sites to explore and develop new approaches along the lines I have recommended. The best of these could be adopted to enable migration to a more effective and efficient system. The Office of the Inspector General made these points in 1999 and again in 2001. Its report called for "re-engineering the federal oversight process." It is time we listen and get on with the job.

Do we have the necessary well-qualified, well-intentioned and committed investigators today?

Yes and no. Most investigators are well intentioned, and, increasingly, they are better trained and qualified. After a few trials, they have demonstrated some commitment to clinical research. Still, 80% of investigators who do one trial never do another — that is hardly what I would call a profession! Although more investigators are now required to have rudimentary training in bioethics, responsible research, and human subjects protection, this training covers only a small fraction of the investigators' knowledge-base and responsibilities for conducting clinical studies. We are seeing the pharmaceutical industry —

both the companies and the regulatory agencies — begin to make noises about requiring investigators to demonstrate training and competence in good clinical practice, that is, GCP. Some companies like Pfizer and Sanofi-Aventis are taking the lead — Pfizer has officially recognized the Certified Physician Investigator (CPI) exam offered by the Academy of Clinical Research Professionals as an important tool for validating investigator competency in GCP. The issuance of a Statement of Clinical Investigator Competence by the Academy of Physicians in Clinical Research is a step in the right direction.[2]

What we have called "human subjects protection" needs to be looked at in a different light. We need to think much more in terms of ensuring the safety and well being of research subjects as a responsibility shared by everyone involved in clinical research. However, the primary responsibility should fall on the investigator. If researchers were properly trained and motivated to take on these responsibilities, with IRB and sponsor support, we would have a much more collaborative, effective, productive and, yes, professional system.

What are the chances?

Many thousands of people are heavily invested in the current system and, despite its shortcomings, it is all we have currently, so we can't expect to completely abandon it any time soon. However, we should start some experimental pilot programs to identify, credential and ease the burden on well-qualified, well-intentioned and committed investigators as a first step toward migrating from our failing compliance-focused approach to a professional-based system. FDA's 2011 guidance on risk-based monitoring suggests some flexibility, and the ANPRM itself, as well as the Presidential Commission for the Study of Bioethical Issues, acknowledges the need for change.

Study sponsors from industry will be very cautious. We can't expect them to risk tens or hundreds of millions of dollars without very clear indications from FDA, OHRP, etc. However, with the necessary regulatory blessings, study sponsors should leap at the chance to conduct studies that attract the best investigators and research teams. The best investigators should take the lead.

References

1. "Greg Koski on Human Subjects Protection," Norman M. Goldfarb, Journal of Clinical Research Best Practices, September 2007.
2. "Statement of Clinical Investigator Competence," Koren, MJ, Koski, G, Reed, D, et al. The Monitor 25(4): 79-82, 2011.

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