

IRBNET INTERVIEW SERIES

Hard Choices for IRBs: The IRB Third Wave

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IRBNet Interview Series

The IRBNet Interview Series is meant to inform and provoke thought on key IRB issues. Through this series we will continue to probe issues of importance to IRBs and interest to the community. Please contact news@irbnet.org with suggestions for future topics or individuals to interview.

Andrew Olmsted, MBA

Andrew Olmsted is Director, Member Services and Development, at IRBNet.

About IRBNet

IRBNet is the most widely used web-based solution to manage federal ethics compliance board requirements governing biomedical and behavioral research, as well as other critical committees and boards. IRBNet's Member community includes universities and colleges, community hospitals and larger hospital networks, and select Federal and State agencies.

We ask Dr. Greg Koski to share his thoughts on critical issues IRBs face today. In our far-ranging interview, we explore the next wave of IRB reorganization (go it alone, outsource, join a cooperative arrangement), the difference between compliance and raising the bar for ethical treatment of human subjects, and choices senior management face today. We close with a glimpse of Dr. Koski's vision for a global approach to clinical research and ethics.

CONTEXT: THE PAST 10 YEARS

Andrew Olmsted: For context, I'm going to describe two waves of change that have taken place in the world of IRB and the management of the ethics review for humans.

Wave one was a handful or ten years ago when we saw the proliferation of commercial IRBs coming into existence as an alternative to using local IRBs for review, either for multi-site research (where you want it reviewed once) or commercial work (where for various reasons folks decided that it might be either more cost effective or provide better quality of review), or for some other reason they wanted to outsource some of their operations to another entity. One outcome of the first wave is the number of commercial entities out there that make their living doing this - Western IRB being perhaps the oldest and most well known in the U.S. - but there are many others. The second wave I describe as the response from institutions over the last few years that have watched this change taking place, have considerable pressure on themselves to respond, and are trying to make decisions. And so it's in this context that I was hoping we could chat. Is that a reasonable way to describe these waves?

Koski: Well, I think it's fine to separate it into wave one and wave two although there may have been many other waves, if not tsunamis and ripples, along

the way. I think that in the first wave you described is largely accurate, although it began well more than 10 years ago. The drivers were also a bit different than the way you characterized them. The independent IRBs basically grew largely out of the need for efficient review of studies that were not under the traditional institutional model that had been set up at or by NIH, HHS. These non-institutional IRBs instead were dealing with studies that were being reviewed and approved largely for industry, corporate sponsored studies that were primarily under FDA oversight rather than, well, at the time it was OPRR oversight, now OHRP oversight. In fact the so-called private or independent IRBs (hopefully all IRBs are independent), the private and often for-profit IRBs, were focused primarily on reviewing this industrially sponsored clinical research or other private sponsored research that did not have U.S. government support or funding and therefore came under a different set of regulations. There's a slight difference there but indeed, as history progressed, we found that when institutional IRBs actually began to get into trouble or recognized shortcomings in their own processes, institutions did begin, as you said, to turn to some of these independent IRBs in order to supplement what could be provided within the institution by its own structure and resources. So apart from that clarification, I think you're pretty much characterizing the situation fairly.

THIRD WAVE: DYSFUNCTION AND REFORM

- Koski: I think we have definitely entered what might be a third phase where many of the institutional IRBs in particular are under really intense pressure for reform as they are increasingly characterized as being dysfunctional. Indeed, the recent article by Robert Levine and Norm Fost in JAMA¹ emphasizes that, referring to the current situation as “dysregulation” of human research in the U.S. So I think we certainly are on the crest of a new wave that's going to require additional changes, both in terms of quality and efficiency of the review and oversight process.
- “... we have definitely entered what might be a third phase where many of the institutional IRBs in particular are under really intense pressure for reform as they are increasingly characterized as being dysfunctional.”*
- Olmsted: Let's pick up on that thread of the third wave. There are tremendous pressures being placed on both large and small institutions that are facing this challenge. What are the alternatives that you see for riding this third wave?
- Koski: Well, I see the current pressure for reform particularly having an impact at smaller institutions or organizations where there has been a realization that running a truly first-

¹ The Dysregulation of Human Subjects Research, Norman Fost, MD, MPH; Robert J. Levine, MD JAMA. 2007;298(18):2196-2198.

class process costs an awful lot of money. It takes an enormous commitment of resources, both financial and human, that these places are increasingly finding is really not available. It's beginning to raise questions as to whether or not these institutions ought to try to continue to have their own internal process or whether they ought to be looking to some other form of cooperative review or collaborative review or even to rely upon an independent review board.

I think in part this is being driven by the fact that accreditation is rapidly becoming the recognized standard for human research protection programs, just as happened in animal review and oversight over 30 years ago. Once accreditation of animal review committees became the expected standard, institutions either had to maintain a committee with that degree of quality or they had to get out of the review business and rely upon someone else. The same thing is happening now in human research as virtually all of the major independent review boards and the human research protection programs at the major academic institutions are all moving toward accreditation.

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And, frankly, it may not be easy for smaller institutions to do so in a cost-effective way. That is, in a sense, a double-edged sword. On the one hand it means there may be less dependence upon local review and more reliance upon some kind of collaborative review. But at the same time it means that the overall standard for review and oversight is also increasing. I believe that's a positive step, one that significantly outweighs the

down side of having less local review. There's really pretty compelling evidence. Studies in which multiple reviews of a single research proposal have been done at multiple institutions reveal that there's a lot of idiosyncratic behavior that goes on among these boards, behavior that is really not contributing anything meaningful to protection of human subjects and is actually probably contributing more to delays in the process and may even be confounding the effectiveness of the process. So, while it's going to take awhile for all of this to shake out, the trends are toward fewer review boards with higher quality systems in place.

Olmsted: So it's a slippery slope. If you're at an institution that takes pride in its human research activity, can you justify the outsourcing of the IRB review process to an organization that does not understand the local context of what's taking place?

Koski: Well, there's an implicit assumption in your question, the way it was phrased, that's just wrong.

Olmsted: Okay, please help me rephrase it.

Koski: Yes. The assumption that outsourcing to an independent IRB means that they're not going to be familiar with the local context of the research may not be correct. Clearly,

both federal regulations and all reasonable expectations of what an IRB or an ethics committee does would require that there be an understanding of the local context. So whether the review is being done by an independent IRB, whether it's local or distant in nature, they have to have effective processes in place in order to ensure that local context is appreciated and respected. But, again, this is one of the concerns about the

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IRB process as it exists today. IRBs oftentimes, particularly local IRBs, end up focusing on local issues that have little or nothing to do with ethical aspects of the research. They have to do with peculiarities of the conduct of research in that local setting and that's somewhat out of the mainstream of what IRBs ought to

be doing in the first place. They really are supposed to be focusing on the ethical aspects of the research and protection of human subjects. Your question, or the way you asked it, implies that independent IRBs aren't going to be in touch with the local environment. And I don't think that that's necessarily true or fair to those entities. After all, many IRBs, particularly the independent ones or the institutionally based IRBs that are reviewing for other organizations, really go to great lengths to try to ensure that there is appropriate consideration of local context.

Olmsted: I agree with you that it was the wrong phrasing of the question. To what degree is being too close to the situation actually a problem? There are times when other considerations come into play in a local IRB review, which perhaps shouldn't be there, and you've highlighted that.

Koski: Sure, of greater concern to me is the increasing complexity of many of the protocols that IRBs are seeing today, a good example being some of the very complex multi-center oncology protocols that are done nationally. Many of these are supported by cooperative oncology groups. These protocols are very sophisticated. Enormous effort and expertise goes into their design, including careful consideration of statistics, and the scientific elements, of the protocol. And many local institutions may lack the expertise to properly review those protocols.

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That's exactly what led the National Cancer Institute to move toward the creation of what I have called a tandem model for review. Others call it a central model. This is a system I know well because while I was director of OHRP I worked closely with the National Cancer Institute to help design it. It's a system that relies upon two levels of review. One that is central, a high-level review that looks in a very critical and thorough way at the scientific as well as ethical and safety aspects of a protocol. That review is then shared with local sites where the local resources focus on those things that are of importance locally, not so much on the ethics and scientific design, because those have already been carefully reviewed. The question for the local reviewers is not so much one of ethics or scientific design, but rather, do we have the

right personnel, both in terms of investigators and support staff? Do we have the right facilities? Do we have the right equipment? Can we do this study at our site appropriately? When one combines that local knowledge of the resources that are available at the institution with the high-level scientific and ethical review, then you have a system that is taking advantage of the best of both worlds. Of course, when you have a study that's going to be done at a few hundred sites across the country, it's important to be able to coordinate the activities at those sites. That, of course, takes our discussion to a topic that's clearly near and dear to your heart, the appropriate use of information technology in order to support this process.

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IRB CHOICES: COMPLIANCE OR HUMAN SUBJECT PROTECTION

Olmsted: You're right. It is critical to have that kind of visibility and oversight when you're dealing with a multi-local type of situation in a networked infrastructure. But first, I want to come back to another point that you raised and push on a little farther. In the context of the third wave, let's say you are a director of compliance at a small to mid-sized research institution that does a combination of commercial work with non-government funds, as well as a mixture of government funded and investigator initiated activities. These individuals are under extreme pressure from a series of parties, from the research side to the administration of their institution, managing the board and what have you. What words would you say to them about what they could do in this third-wave world that we're living in?

Koski: Well, I guess I'd have to preface my remarks by saying that I would never put myself in a position of director of compliance because that's not a position that I find as meaningful as one that's really looking at the true goal of protecting human subjects. There's a big difference between complying with

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regulatory requirements and protecting human subjects. But nevertheless, the two clearly go hand in hand.

One of the major criticisms of the entire system currently is that it focuses far too much on compliance with regulations, without dealing in a meaningful way with the real issues of human subjects protection; the focus on compliance can become a

distraction from the real goal. And indeed, it often leads institutions -- or their IRBs -- to do things that may not be either in the best interest of the institutions or in the best interest of the research participants.

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So with that as a backdrop, I agree that clearly every IRB, independent or institutionally based-and the "I" works for both of those-has to comply with regulations. But that's the absolute minimum standard. If you go below it, then you're basically a crook - you're breaking the law, and that's an unacceptable place to be. Simply trying to achieve one-hundred percent compliance with

regulatory requirements is really just the lowest acceptable level. The real goal is to get beyond compliance.

BEYOND COMPLIANCE: TECHNOLOGY IMPACT

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The big question is what can we do in order to help us move this whole system beyond compliance - not only improve the thoroughness and the quality of the review, but also the efficiency of the review process and the effectiveness of oversight. My own view has long been that if we can effectively use tools that are already deployed in other settings, tools known to be highly effective to support safety-focused systems, these tools can actually facilitate the process. One can streamline operations in a way that allows resources that would

otherwise go into simply turning the crank, to be devoted to doing things that are more substantive in terms of the actual process of protecting human subjects.

This is one of the areas where information technology becomes very important and is known to be effective if it's used appropriately.

The National Council of University Research Administrators, or NCURA as it's called, held its first conference on electronic research administration all the way back in around 1992, when there were several institutions in the country looking at how we could use information technology to actually improve the process, not just to manage the paperwork in electronic form, but to actually use information technology as an adjunct to extend the human capability. Look at an area such as adverse event reporting. As individuals put data into the system by reporting an event,

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a well-designed system works as an artificial intelligence engine, one that can look at those data and detect when a significant event occurs, either at one site or at multiple sites and make it possible to provide an early warning system, similar to having an early warning radar system. A lot of these ideas about how to more effectively utilize information technology have been around for a long time.

But even today, many of them are not being taken advantage of fully. The major uses of information technology to try and improve the process have focused on operations-- developing electronic submissions, often which involve creating forms that are electronic that have built-in reminders if required information is overlooked. And these can certainly be helpful. In fact, smart wizards to help develop applications whereby filling in a series of questions generates paragraphs of text that can be automatically formatted into a standardized application. All of these tools can streamline the process, not only for submissions but for review, because all of the information comes out in a formatted form that the committee expects to see and they know where to look. So it can facilitate the whole process. This is precisely what the FDA is trying to do with its emphasis on EDC (electronic data capture). Again, many institutions recognize that the tools are there to do these things. But they're expensive and there're not that many institutions that have the in-house expertise, or the money, to develop and deploy these kinds of systems. So, with a demonstrated need and capability for doing this and, there are now several companies that have stepped up to try and build systems that can be used out of the box to help improve the process. And that is a very good thing.

Olmsted: Often times, when people make a decision about technology infrastructure in light of trying to make an impact on their organization -- and I'm speaking of IRBs and other committees now -- the first question I'm typically asked is how much does it cost? But in light of all the things we've been discussing, there's a much bigger picture here. It starts with 'What can we do to raise the bar on this oversight function and do right by the research?', moves to 'How does our organization do it cost effectively and efficiently?' and moves then to 'How do we scale this operation for growth to the future?' And now we are experiencing this third wave - go it alone, join some form of cooperative regional activity, or outsource activities to an independent board. Those are a lot of decisions that folks need to make. Do you have any words of advice to them?

Koski: Well, I think the most obvious one is that if you're not taking advantage of information technology to support and facilitate your processes then you've missed the boat. You can look at every small business in the country. Most have recognized that they have to have a presence on the web, even if it does nothing more than give their phone number and contact information, and perhaps a map to their location. It's just the

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nature of getting things done today. We're increasingly becoming a world that's dependent upon electronic exchange of information and using information technology to keep it organized and flowing smoothly. So I think human research protection programs need to get there and the sooner they get there, the better off they and the overall system are going to be.

To draw back to our earlier question about compliance, clearly information technology can facilitate compliance. If one looks at the cost of adopting an information technology platform that can facilitate compliance relative to the cost of having one episode of serious non-compliance that's picked up in an FDA audit or results in serious harm to a research participant, it's very clear that this is an investment that is very valuable that should be made. Just looking at the costs is a mistake. One has to consider the cost of implementing or adopting this kind of technology as an investment. The efficiencies that can accrue to institutions that adopt and effectively use information technologies can result in more research activity coming to their institution, which certainly has positive spinoffs as well. So, a single word of advice would be to recognize that this is no longer just an opportunity; it's almost a necessity, and institutions should move in that direction.

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FUTURE VISION: TECHNOETHICS AND A GLOBAL HUMAN RESEARCH NETWORK

Olmsted: You've been very patient with your time, and I want to ask you one more question. Where, both on a national and international basis, are the opportunities for greater oversight and harmonization of activities? Certainly pharmaceutical companies funding research and trials are global. And there are lots of efforts, of which you are certainly familiar with several, to harmonize the oversight of some of these functions. Can you share with me one vision you have for how these things start to come together?

Koski: Thank you, Andy. I relish the opportunity. For almost a decade now, I've been not only thinking about but talking about the analogy between the international aviation safety system and human research, particularly the systems infrastructure for support of safety--a vision I continue to promote. That vision is to build an international network of accredited research sites, all operating under fully accredited human research protection programs with professionally trained and certified individuals, all working according to internationally recognized and accepted standard operating procedures and guidelines. The groundwork is already being laid.

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We see it in the widespread adoption of the International Commission on Harmonization's Good Clinical Practice guidelines, the ICHGCP. But we need to move well beyond guidelines, because, as clearly you said earlier, clinical research in particular is already very much an international activity and moving toward becoming a global activity. Right now, it's more international than global; being international means it's being done in different ways in multiple countries around the world, but if its to be done in a global way, there has to be more interconnectivity and standardization of those

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individual national efforts. There's enormous concern that much of the so-called outsourcing of clinical research to areas that are described either as developing countries or emerging markets, depending upon how one's looking at it, are fraught with potential problems because many of the countries where there is rapid growth of clinical research activity don't have a longstanding tradition in clinical research or appropriate systems, either regulatory or ethical, in place for oversight of that research. Many lack the kind of infrastructure necessary to support it, and yet companies in particular, as well as government-funded researchers, want to move into these areas to do work. Clearly, they would benefit from this, and want to see it done correctly. Building a global network for human research along the lines that I described, one that could use a shared information technology system as its foundation, would

enable us to not only have a study reviewed and approved but have it up and going quickly at multiple sites that are all operating according to internationally recognized standards. Connection of these sites by a global information network would ensure that there is not only effective processing of information but also monitoring of adverse events, thereby both enhancing efficiency, quality and safety as the research goes forward, in much the same way that we have developed a global air transportation safety system. This would be the my ultimate long-term goal and my vision - that we could build this global safety network for responsible human research that will allow us to really bring the benefits of clinical research to the entire world in a safer, more efficient fashion than we can today.

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Olmsted: Dr. Koski, thank you very much for your time. And on behalf of all the readers, we thank you.

Koski: Terrific. It's always fun to talk to you, Andy.