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Major Ohio research institutions create nation's first CTSA IRB collaboration

Collaboration could enhance biotech growth in state

Three large Ohio academic Clinical and Translational Science Award (CTSA) institutions recently formed an IRB collaboration to allow a central IRB review during multisite studies. This was the first time CTSAs collaborated in this way, and it could serve as a best practice for other research institutions and CTSAs, experts say.

Case Western Reserve University in Cleveland, the Ohio State University in Columbus, and the University of Cincinnati agreed to allow one institution's IRB to conduct human subjects research reviews for other institutions during some multisite studies.

"We wanted to create a clinical research powerhouse so companies or the National Institutes of Health or research organizations could come in and assess how many patients were available for a study, and we could rapidly get things up and running on the IRB," says **Pamela B. Davis**, MD, PHD, dean and vice president for medical affairs and Arline and Curtis Garvin research professor at Case Western Reserve University School of Medicine.

The IRB review collaboration could pave the way to far bigger research gains across Ohio by providing greater speed and efficiency in multisite study reviews, says **Charles Lockwood**, MD, dean of the Ohio State University College of Medicine.

"By lowering the barriers of entry, it might generate significantly greater numbers of grants," Lockwood says. "It will be a very powerful tool for obtaining external funding and generating more internal funding, as well."

Ohio research institutions and state leaders have worked to increase the volume of research to enhance its already robust clinical trial and grant economic stimulus, he adds.

"The number of people employed due to clinical trials in the

state is around 80,000, a substantial number," Lockwood says. "We have $850 million a year in funding for clinical trials in the state, and there are an estimated 4,000 current clinical trials statewide."

Research is becoming an economic engine for Ohio, which traditionally has been an agricultural and manufacturing state.

"It's also generating knowledge and creating the ability to ensure that critical masses of investigators are present in various state facilities, and with that comes the additional abilities to recruit additional people and create more research potential," Lockwood says. "This allows the state to generate biotech as a significant source of growth and then develop our own biotech companies."

The three Ohio institutions do the majority of research in the state. Their CTSAs expect them to network, and the collaboration is a good example of their working well together, says **Thomas Boat**, MD, vice president for health affairs and dean of the University of Cincinnati College of Medicine.

"This is probably a really good example of how institutions can work together to facilitate clinical research," Boat says. "You need a big patient population for clinical research, so getting multiple institutions involved is important and mandatory for certain kinds of studies."

Another benefit is that the collaborative agreement could serve as a model for CTSAs in other states, and the action could result in high marks when each of the three CTSAs comes up for renewal, Boat suggests.

"This opens up our investigators to access at clinical trials in other institutions, and vice versa," he adds. "We could develop a broader array of clinical research activities at our institution."

The idea of a collaborative agreement was initiated more than a year ago, Davis notes.

One key to its success was the investment in an electronic hub that expedites the IRB review process by making it easier to transfer large documents, she says.

"When we first developed a facilitated review, we discovered part of the delay was in sending documents because they are so big and when they're downloaded they can get into a clogged system," she explains.

With the hub, the documents are more easily downloaded in the right format, and IRBs can work more quickly to process the information.

"It incrementally speeded it up," Davis says.

"We went to the state and were challenged by the governor to leverage the power of CTSAs across the state, and this seemed an obvious opportunity," she says. "At a

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meeting with the governor in August 2011, the CTSAs spoke up and said, 'We have a great infrastructure, and we think we could work together,' and the governor said, 'Come back to me and show me how you can do it,' and so we did."

"We started doing facilitated reviews across the state and then thought, 'Why stop at facilitated?'" Davis recalls.

The Endocrine Society of Chevy Chase, MD, heralded the Ohio CTSA collaboration, saying it fit in well with the society's 2011 position statement on the use of central IRBs (CIRBs).

"In an effort to streamline the IRB approval process for endocrine-related studies and others, improve consistency, and assure accountability, the use of central IRBs has been suggested for multicenter clinical research studies," the Endocrine Society's position paper of June 2011 states.

"The Society strongly encourages the utilization of CIRBs for multicenter clinical studies in order to advance clinical research and improve patient care while maintaining the highest patient safety standards," the position statement says.

The Office for Human Research Protection (OHRP) also endorsed the idea of using a single central IRB for multicenter research in a letter written to Carolinas Medical Center of Charlotte, NC, on April 30, 2010: "I want to assure you that the Office for Human Research Protections fully agrees with FDA's position on the benefits of relying on a single central IRB for multicenter research," writes **Jerry Menikoff**, MD, JD, director of OHRP.

Collaborations that produce a central IRB for review of multisite studies also fit in with accreditation goals, says Boat, who is a past president of the board of the Association for the Accreditation of Human Research Protection Programs (AAHRPP).

As a member of AAHRPP's board, Boat has worked to find ways to enhance research without throwing up obstacles. The collaboration fits that philosophy, he says.

"What's clear is that at research-intensive institutions, IRBs have a huge load put on them," Boat says. "This will reduce the work, create better efficiencies, and probably allow one institution to more thoughtfully look at all dimensions of a study and share the outcome of that process with other institutions."

The collaboration was embraced by each institution's IRB, researchers, and others, Boat, Lockwood, and Davis say.

"Everybody locally and across the state I have talked to has been uniformly enthusiastic and laudatory about this," Boat says.

Small hospitals in Ohio already have contacted Case Western Reserve about joining the collaboration, Davis says.

"The first requirement is that all the IRBs be accredited by AAHRPP, which elevates the IRB to the level of meeting certain standards," she adds. "I'm very enthusiastic about the potential; this is one example of the potential of CTSAs to change how we do clinical and translational research, and the public should know the academic community is working hard to bring new drugs, new therapies, and new strategies to them as quickly as possible and without sacrificing protection."

While each institution will retain the right to have a local IRB review whenever it finds a study to be particularly complex or for other reasons, there likely will be a great deal of shared study review, according to the three university deans.

Since this more efficient IRB review process will free time in each of the universities' IRB offices, there is the potential for taking on more research reviews and work, they say.

"We anticipate more business," Lockwood says. "I see this kind of arrangement as being critical to going forward."

The three Ohio CTSAs have taken a good step toward reducing the energy barriers to doing multicenter studies, he says.

"If we really want there to be greater collaboration from Cleveland to Cincinnati and including Columbus, Dayton, and Toledo, and other schools, then we need to do more and do more together," Lockwood says.

IRBs work hard and often put up with backlogs. The collaboration will help them clear their agendas and become more efficient in reviewing protocols and reducing study delays, Davis says.

"Having a uniform set of expectations and guidelines puts the state in the right direction and allowed Ohio to put together this IRB," Boat says. "This will enhance the overall number of studies done, but hopefully it also will allow us to do more studies without spending a lot more money or wasting IRB members' time." ■

Evolving Internet means new ethical issues

Challenges to keeping up with technology

One of the biggest challenges IRBs face is keeping up with ethical issue updates during an ever-evolving period technologically, experts say.

"These new technologies are pushing the boundaries of traditional research and research ethics," says **Elizabeth A. Buchanan**, PhD, endowed chair in ethics and director of the Center for Applied Ethics at the University of Wisconsin-Stout in Menomonie. Buchanan also is the associate editor of the *Journal of Empirical Research on Human Research Ethics*.

Social media used for research studies is one example, she notes.

"There is a ton of Facebook pages and YouTube streams that run the gamut from data collection to dissemination of information," Buchanan says.

One chief conflict involving electronic data and research is the complexity of handling de-identified data within an Internet landscape where re-identification is easier than ever before, says **Joe Konstan**, distinguished McKnight professor and distinguished university teaching professor in the department of computer science and engineering at the University of Minnesota in Minneapolis.

The issues include data that are inherently self-identifying even when researchers take names off the data, and the problems of search logs in which data can be re-identified based on the searches. The potential for these breaches in electronic and computer security is greater than for stored files in a locked cabinet, he notes.

Buchanan and Konstan outline some of these major ethical challenges IRBs face in reviewing studies involving electronic data and Internet research:

• **Cell phones and privacy:** Just two years ago, the cutting edge of new technology involved Internet social media sites. While those still thrive, the latest technological changes have to do with the use of cell phones and mobile apps, Buchanan says.

"On that front, you have issues that bring us back to major concerns like privacy and dissemination of data; is it encrypted when shared with a mobile app?" she explains.

On one hand, mobile technology has created great opportunities for researchers to capture real-time data. For example, an investigator could send out a question asking a subject what he or she is feeling or doing right now, and the answer could be immediate and honest.

"It's giving researchers very interesting access to subjects synchronously," Buchanan says. "The subject just texts back and some mobile application has their responses; it's really moving research forward."

But there is an ethical issue to this type of use of mobile technology. "We have to think through the privacy, confidentiality, and data security issues that come along with these emerging forms," Buchanan says. "And depending on the sensitivity of the data, do we want AT&T or Sprint to be the holder of our data, which is the case when we're using our cell phones?"

IRBs have to inquire about the safety of cell phones when they're used to collect data. There are solutions, such as remote lockdowns in which someone can close access to a phone's data when it's lost or stolen, she adds.

Mobile technologies often rely on grid computing in which data are maintained in cloud storage, meaning an off-site location. This also poses security and privacy risks, Buchanan says.

"Questions IRBs are asking have to do with the security of the cloud," she explains. "Is it a private cloud such that only the researcher has an access key to it, and how are we going to ensure when we put data on a Google document that we're giving data only on Google?"

It's these practical issues that matter from an IRB's perspective. And sometimes the solution is a disclaimer, such as the one written at Penn State: "Your confidentiality will be kept to the degree permitted by the technology being used. No guarantees can be made regarding the interception of data sent via the Internet by any third parties."

With the relative ease of data transfer and greater potential for security issues or inadvertent disclosures, research informed consents now use language that reflects the new reality and emphasizes limits to confidentiality, Buchanan says.

• **Electronic medical records and re-identifying data:** "In the last few years there has been a huge amount of re-identification of

seemingly de-identified data," Konstan says.

The challenge is using datasets with personal information in a way that protects the personal information while still making it available for research, he adds.

Medical record data contain a lot of self-identifying and sensitive information, Konstan says.

"Even pieces that seem harmless may not be," he explains. "You have a date and time for a procedure and the record notes where it was done."

Someone who knows the subject might be able to determine who the person is based on that kind of information, he says.

For instance, there was a radiology report that discussed a patient's drug abuse and history of domestic violence, combined with the exam that noted a potential incident of domestic violence, Konstan says.

"There was enough information in that report that if a person who was a spouse or domestic partner of the patient had seen the de-identified report, it probably would have been obvious that the patient had talked with people at the clinic about what had happened," he says.

There were no security breaches, but this example illustrates how difficult it is to de-identify medical records, particularly when electronic records make it far easier to search for specific details about patients and potential subjects.

• **Facebook and YouTube subject recruiting:** Pfizer's Research on Electronic Monitoring of OAB Treatment Experience (REMOTE) trial was a completely virtual trial that conducted subject recruitment via Facebook from June 2011 to June 2012. Subjects received medications at their homes and used an electronic app to keep diaries and report outcomes. The trial's purpose was to compare a virtual trial with a traditional trial, according to CATO Research at www.ask-cato.com.

"Pfizer set up a designated Facebook page to recruit subjects," Buchanan says. "Participants communicated with the principal investigator via Facebook and electronic means, and then they had regional sites where people could go for testing and to get blood drawn."

It is becoming more common for clinical trial sites to use Facebook, YouTube, and other social media as part of their recruitment strategies, she notes.

"It's fascinating because you see everything you could imagine," Buchanan says. "Depending on what the trial is, they will use social media in interesting and unique ways, including putting out a YouTube video or Twitter stream."

Just type in "clinical trial recruitment" in the YouTube search engine, and a wide variety of videos pop up. One of the first is a video called "Playing the Clinical Trial Recruitment Game," by a self-proclaimed human guinea pig. This suggests another ethical issue IRBs should consider: fraud in online recruiting. If the study involves an online survey with a relatively high participant incentive — and $100 might meet that threshold for many people worldwide — it could attract an influx of people who are not true potential research subjects, Konstan says. *(See story about online recruitment fraud, below.)*

IRBs also might question the role trust plays when participants are recruited through the Internet and social media sites.

"It's a different mentality of researchers coming to participants rather than having them come to us through a doctor," Buchanan says. "It raises the issue of do we trust a YouTube video versus our doctor saying there's a clinical trial." ■

Potential of fraud in online recruiting raises red flags

Watch for link hijacking

Researchers using the Internet for recruitment and for electronic surveys have discovered that problems with online fraud can undermine the ease and efficiency of Web-based recruiting, an expert says.

"It's a huge problem that online surveys with significant competition have high fraud rates," says **Joe Konstan**, distinguished McKnight professor and distinguished university teaching professor in the department of computer science and engineering at the University of Minnesota in Minneapolis.

This can undermine the research and result in invalid results, he explains.

"I've seen examples of studies where they had to throw out well into the double-digit responses because they detected fraud," Konstan says.

"If it takes 10,000 responses to get 1,000 valid ones, it might be okay," he adds. "But if you take 10,000 and think you have 1,000 valid ones when in reality you might only have 100, is it worth putting subjects to any risk whatsoever when you can't count on the data you're getting back?"

This is the sort of question IRBs should consider when reviewing a survey that will rely on Internet recruitment.

"If results are sufficiently in doubt, there might not be any benefit," Konstan says.

IRBs could suggest a few precautions to reduce the risk of recruitment fraud, including these:

• **Do not overcompensate.** "Make sure you're not overcompensating," Konstan advises. "Any survey with a compensation of $100 will have a lot of attempted fraud."

• **Make screening more complicated.** Surveys that require potential participants to answer a number of questions before being eligible for recruitment can help reduce fraud attempts.

"Have them go through enough of a process that you have greater confidence that someone online cannot sneak in," Konstan says.

• **Watch for link hijacking.** "A recent study I worked on had a very small population they were trying to reach, and they marketed the study on websites specifically directed to that population," Konstan recalls. "But someone picked up the survey and put a link somewhere that marketed making money online, so this study had a lot of fraudulent attempts — mostly from out of the country."

Sometimes this phenomenon can be observed by examining IP addresses of respondents. However, that is not foolproof. In the case Konstan mentions, the contacts appeared to originate in the United States.

Investigators should check readily online to see if their survey link pops up in places where it does not belong, he suggests.

• **Look for consistency.** "Look for consistency across different sessions, and if those do not match, this should raise flags," Konstan says. "Have principal investigators constantly screen for fraudulent responses."

• **Look for sloppy responses.** Respondents who rush through the survey could be part of a fraudulent scheme, he says.

• **Hire professionals.** "Another way is to have a professional survey center handle this for you," Konstan says. "You design the survey, and they'll do it." ■

BEST PRACTICES SPOTLIGHT

Study map can support informed consent review

Use pictures, diagrams

Informed consent forms have one very daunting characteristic: They are visually numbing.

In addition to their many pages, medical terminology, legalese, and often higher-than-desired reading grade level, they are simply boring to look at, an informed consent expert suggests.

"I'm a visual person," says **Megan A. Foradori**, RN, MSN, a contractor with the Henry M. Jackson Foundation for the Advancement of Military Medicine and research agenda project consultant for the TriService Nursing Research Program of Bethesda, MD.

Foradori presented informed consent information to subjects for a recent study of decision-making and recovery among living kidney donors conducted at the Johns Hopkins University School of Nursing in Baltimore, MD.[1]

She sensed that they were nodding and smiling, but not retaining the IC information.

"So it made sense to make a picture," Foradori explains. "Our principal investigator thought it was a terrific idea."

Foradori found simple icons and then added words. The illustrations evolved into a single-page study map that is designed like an illustrated flow chart. The map contains simple bar-stick figures representing the research participant. At its top is a thought bubble, reading "Decision Making & Health," leading to the participant. An arrow points to the figure and says, "This is you in clinic today."

The study map contains these sections, each with arrows leading to them:

• A circle containing an illustration of two written pages and the words, "At your visit, today, we will go over the informed consent sheet. By signing this, you say that: You understand the information given; You agree to the conditions; You will participate in this study."

• An identical circle has dialogue saying, "Decision-making, your health, family relations, how you learned about donation, your ideas of the

risks and benefits for you and the recipient."

• Connected to the decision-making circle is a circle with a folder in it, saying, "I will access your hospital records to learn about your health."

• Following that, the flow chart divides into two sections, with the first for participant who agree to fill out a survey and donate kidneys and the second for those who do not donate.

• It follows with a list of graphics illustrating what will happen at three months after surgery, six months after surgery, and one year after surgery; or three months from today in the case of those who do not donate.

• It ends with a box, saying, "Interviews for some participants, both donors and non-donors, in person or by phone at your convenience (we will contact you).[1]

"We enrolled participants who were considering donation but had not yet given approval," Foradori says. "They filled out a survey, and we made sure they understood there were two arms to the study and even if they were not selected, we wanted to hear from them two months after donation."

Thirty research participants were randomly assigned to a standard care group in which they received a verbal description of the study and written consent documents or an experimental group that received the standard of care plus a study map. The study found that all participants demonstrated high knowledge levels of the informed consent when given a simple quiz about the study.[1]

The participants were highly educated, with about 77% having had some college education, she notes.

"They had a high level of understanding of the study in both groups," she says. "People in different educational levels would have benefited more from a schematic."

There were intangible benefits from using the study map.

"Not only did the study map help research participants understand the study, it ensured new research nurses gave each person the same information," Foradori says. "Every participant received the same information, and the study map helped make that happen."

Using a visual study map could prove helpful for future studies and informed consent processes, she suggests.

"If people could have more visual representations of the decisions that need to be made in health care, the study map could help them make great decisions," Foradori adds.

REFERENCE

1. Foradori MA, Nolan MT. Effect of a study map intended to support informed consent in transplant research. *Prog Transplant* 2012;22(1):56-61. ■

Sound studies assured with scientific review

Process improves protocols

To ensure that a proposed study or clinical trial can fulfill its goals and remain within ethical guidelines, some IRBs have mandated that protocols go through scientific review prior to submission. The purpose of the review is to ensure that studies are built on a solid scientific foundation to achieve the objectives.

"The biggest issue we have that I think holds up approval is the quality of the research design," says **Mark Schreiner**, MD, chairman of the committee for protection of human subjects at Children's Hospital of Philadelphia (CHOP). "From the IRB's perspective and mine, if a study can't clearly achieve its objective, it's not ethical to start." Scientific review of proposed research has been close to Schreiner's heart, as it was a cause he championed at the IRB of Children's Hospital of Philadelphia. A proposed study that does not have sound science can be a major hindrance to the approval process.

When Schreiner became IRB chairman in 2005 and was running the clinical trials unit, he felt time was being wasted with studies that were not ready for committee. "We can send requests for modifications back, but in resubmissions there were issues still outstanding because the IRB isn't going to give a 20-page list of all the things that should be changed," Schreiner says.

Taking out the frustration

Proposed studies where there were issues with scientific design took longer to approve and were a source of frustration for Schreiner. "Everybody wants the process to be rapid, and it's not when we get things that are not approvable," he says. "It takes away from people who have NIH [National Institutes of Health] approval and

funding. The weakest 25% of protocols take up 75% of the time." These submission issues sparked the mandate of scientific review at CHOP.

Before a study can be submitted to the CHOP IRB, it must go through a scientific review process. While the exact steps of that process are left up to individual departments at CHOP, the IRB provides example protocol templates for investigators to follow. With the science of proposed studies reviewed ahead of time, Schreiner has found that studies are approved more quickly, with less time spent on IRB members sending studies back with questions and fewer protocols being deferred. "It actually speeds up the approval time to have that extra polish," Schreiner says.

Studies funded through the National Institute of Health or other large granting agencies, as well as industry-funded studies, are not required to go through the review process, as the science is already considered to be sound.

According to Schreiner, a proposed study can look good in every way and have sound goals, but shaky science and an incomplete analysis plan can lead to rejection. The CHOP IRB recently considered studies that looked good on the surface but had underlying issues. "Our IRB recently saw two studies — one inadequately defined numerous issue, while the other had very ambiguous objectives and the analysis plan did not make sense," Schreiner says. "Both were worth doing, but the provided information was inadequate to support sound scientific design — the IRB deferred those. One was approved at other IRBs."

While it took some time for researchers to get the hang of the process, Schreiner says that many excel. "Over the course of the last five years, people have become more sophisticated. It didn't happen overnight, but it's well worth the effort," he says. "Some of our departments have sophisticated people — for instance, the ED requires fellows to get a master's degree, and most get one in epidemiology. There are plenty of people with strong clinical study design as a result of people with that kind of training."

Even minimal-risk studies are subject to review. "The biggest problems right now are minimal-risk studies that don't involve drugs, and the expedited studies," Schreiner says. "A lot of those are descriptive research — not really a problem because no one's trying to do anything grand. Those are so straightforward that they are relatively easy to approve. It's people who have greater ambitions but don't have the help to design [the studies] to take in all the confounding variables that trouble arises."

Though the studies are considered minimal risk, results can still have a great effect on a population if the results are later proven incorrect. "Some people would say, if there's no harm, then no foul in minimal-risk research," he says. "But there are a lot of instances where real harm has been done. For instance, there was a women's study that said HRT [hormone replacement therapy] reduced the risk of cardiac disease, which was later proven wrong when a randomized trial was done. Things like that can result in negative consequences in a large population."

Departments know best

CHOP isn't the only IRB to embrace the scientific review concept. Boston Children's Hospital has a similar approach, with every department having its own scientific review process and the IRB taking more of a background role. "What we decided to do was really embrace the concept that disciplines know the science the best and each department was to develop their own scientific review process for review of protocols before coming to the IRB," says **Susan Kornetsky**, MPH, director of clinical research compliance, Boston Children's Hospital. "Each department had to go on record and indicate what the process was — it could be a committee, or a department asks other colleagues to review. It's completely open-ended."

Though each department at Boston Children's can develop its own review process, the IRB developed a central list of questions for each department to follow. The departments expand on the questions as they see fit. After completion, all evidence of the review is to be submitted to the IRB. "The IRB can still consider the science, and if we have questions, we can send them back to the investigator," Kornetsky says.

As with many new things, there was some initial resistance to the scientific review process — mostly due to how much additional time it would take. "Initially, I think there was concern mostly about the timing," she says. "How much time would this take? I think there was resistance at first, but this mandate really came from the president down, and there was no question that they had to do this. The department chairs had

to sign on, and it was their responsibility to be responsive to their own faculty and develop a process that wouldn't be cumbersome."

Over the years, the IRB has seen significant improvement in the quality of the protocols submitted. "It's very obvious to the IRB members what departments do this really well — the protocols are much better developed and in better shape," Kornetsky says. "They address issues and are well-prepared and have a meaningful analysis section. Some departments don't do quite as well and protocols are a little less developed."

Over time, Kornetsky found an unexpected benefit of scientific review: a chance for the IRB itself to learn and grow. "Often, we will see the scientific review information, and we have found that the research groups are also pointing out issues they had with other IRBs," she says. "Sometimes, they're actually taking that as a step to help other faculty members from their own experience — they'll point out things that have prompted concern, or they'll make recommendations. It's like getting a little bit of free advice. I think many of the comments that are made are very much on target and helpful. We use it as an opportunity for friendly advice."

All in all, the scientific review process has been a boon to the approval process, particularly for Schreiner. "To me, it takes so much effort to do clinical research well and just as much effort to do it badly," he says. "If we want subjects to go through risks for the benefit of science, we should get something out of it." ■

Elderly subjects can benefit clinical trials

Studies show elderly are often excluded

Researchers and physicians are increasingly speaking out on the issue of the geriatric population being excluded from clinical trials.

A 2011 study in the *Journal of General Internal Medicine* looked at phase III and IV studies conducted in 2007. The research team focused on the age limits of the study and the reasons for exclusion.[1]

"One of the major findings was that 20% of the clinical trials excluded patients on age alone, and nearly half of remaining trials excluded adults that have complex conditions," says **Donna Zulman**, MD, instructor in the division of general medical disciplines at Stanford University, and physician investigator at the Center for Health Care Evaluation at the Veterans Administration Palo Alto Health Care System, and the study's lead author.

Other studies in the analysis had eligibility criteria that disproportionately affected older adults, including medical comorbidities, those living in nursing homes, and physical disability or functional limitations.

"I think it's extremely important for IRBs and funding agencies and the FDA to accept this issue and ensure that, when it's possible, to include geriatric patients, and that age exclusions are for good reasons," Zulman said. "We want to make sure those individuals are well-represented."

Geriatricians and primary care physicians have found it difficult to care for their geriatric patients with new medications. Physicians proceed with caution when prescribing new medications that do not include evidence as to how the drug will affect an older person's system, or interact with other medications.

"Many of my patients are older and have multiple chronic conditions," Zulman says. "The information out there isn't always relevant. Physicians are using more art than science to understand what will work best with patients."

The study concluded, "Clinical trial evidence guiding treatment of complex, older adults could be improved by eliminating upper age limits for study inclusion, by reducing the use of eligibility criteria that disproportionately affect multimorbid older patients, by evaluating outcomes that are highly relevant to older individuals, and by encouraging adherence to recommended analytic methods for evaluating differential treatment effects by age."[1]

"There's a lot of potential there"

As the baby boomers age and near retirement, the health care system will see an ever larger increase of seniors taking medications. The Population Resource Center estimates that the number of people age 65 or older will double by 2030.[2] The over-65 population accounts for about 60% of healthcare expenditures. Life expectancy is increasing rapidly, and one in five Americans will be 65 or older by 2030. With the older population growing quickly, the need for new medications and

an understanding of how they will affect an older population is growing more urgent. In 2005, the American Geriatrics Society found that more than 900 drugs in the trial stage were aimed at treating conditions associated with aging.[3] However, some physicians express frustration that elderly subjects are excluded from trials, and would like to see IRBs insist upon elderly inclusion.

"There will be more elderly in a study if there's a requirement," says **Diana Zuckerman**, president of the National Research Center for Women & Families Cancer Prevention and Treatment Fund in Washington, DC. "If the folks doing the study are told to include the elderly, it will happen. They will do what their doctors suggest. I don't think there will be an 80-year-old more stubbornly refusing than a 40-year-old. Someone who is 80 years old would be less afraid, and more likely to just go along with whatever the doctor suggests. I think the issue is an IRB saying, let's make sure patients in the study are patients who will benefit from the intervention and not just open it to people to a certain age — some percentage [participants] must be in this age group."

One factor in excluding subjects above a certain age is that researchers are looking for the best results from a drug — studying its effects in people with only one condition and focusing just on that condition. And it's not always feasible to include elderly subjects if they are too fragile or the drug too risky.

"The part about this that is understandable and appropriate is that it's easier to understand a product that is used on patients who are healthier, so the study is on patients who have one condition only," Zuckerman says. "But this is not true in the real world. People have a lot of different health problems that are going on at the same time, especially in people over 70.

"I think that IRB folks should care very much what the age range is and what the protocol requirement of comorbid conditions are," Zuckerman continues. "Drugs and devices are tested on people younger and healthier than many of the people who will use it. Those results may be overly optimistic about effectiveness."

As a result, many new drugs are prescribed to older patients who may have many comorbidities and are taking several other medications, without knowing how the new drug will interact. Metabolic systems vary and are more fragile.

For example, a new osteoporosis drug "is being given now to a large number of older people and we have no idea how it will act in an older population," says **John Morley**, MD, director, division of geriatric medicine at Saint Louis University. "Drug companies will tell you that if you put an older person in, the chance of side effects will go up significantly. They want to tell the FDA that a drug is fundamentally safe. They are not drug side effects, just side effects that occur in people with lots of events [comorbidities]."

Zuckerman cites medical devices, such as gastric bands or replacement hips and knees, that may not have been tested in people over 65. "Are they ever tested, and is there a difference for people over 65? If studies don't include those people, how do you know? The effects might be good in the short run, but not in the long run.

"There are numerous instances of Medicare paying for devices tested on younger people with no evidence that they are good for older people," Zuckerman says.

Morley has found there is much willingness among geriatric patients to be part of clinical trials. "There is a lot of interest there as a whole," he says. "If it's a complex trial and the person is very frail, that's different, but in general it's very easy to enroll this population in trials."

Transportation and costs are other barriers to participation by elderly people. Medicare has tried to ease those burdens by paying for routine costs of items and services, including room and board, costs of device implantation, and treatment of side effects and complications. However, Medicare beneficiaries must cover the costs of coinsurance and deductibles, as well as the new item the study is testing.[4]

Morley has seen success with trials that have included older patients. "Occasionally you do see drugs being tested in people to the age of 85, and with positive results," Morley said. "There's a lot of potential if you do it."

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1. Zulman DM, Sussman JB et al. Examining the Evidence: A Systematic Review of the Inclusion and Analysis of Older Adults in Randomized Controlled Trials. *J Gen Intern Med* 2011 26:783-790

2. Population Resource Center. The Aging of America. http://prcdc.org/300million/The_Aging_of_America/

3. American Geriatrics Society. http://www.americangeriatrics.org/files/documents/Older_Adults_in_Clinical_Trials_FINAL.pdf

4. Centers for Medicare& Medicaid Services. http://www.medicare.gov/publications/pubs/pdf/02226.pdf ■

CNE/CME OBJECTIVES & INSTRUCTIONS

The CNE/CME objectives for IRB Advisor are to help physicians and nurses be able to:

- establish clinical trial programs using accepted ethical principles for human subject protection;
- apply the mandated regulatory safeguards for patient recruitment, follow-up and reporting of findings for human subject research;
- comply with the necessary educational requirements regarding informed consent and human subject research.

Physicians and nurses participate in this continuing education program and earn credit for this activity by following these instructions.

1. Read and study the activity, using the provided references for further research.
2. Log on to www.cmecity.com to take a post-test; tests can be taken after each issue or collectively at the end of the semester. First-time users will have to register on the site using the 8-digit subscriber number printed on their mailing label, invoice or renewal notice.
3. Pass the online tests with a score of 100%; you will be allowed to answer the questions as many times as needed to achieve a score of 100%.
4. After successfully completing the last test of the semester, your browser will be automatically directed to the activity evaluation form, which you will submit online.
5. Once the completed evaluation is received, a credit letter will be e-mailed to you instantly. ■

COMING IN FUTURE MONTHS

- ■ Simplify informed consent forms using these strategies
- ■ Study shows positive results from use of Web-based informed consent
- ■ Issues with reviewing adaptive design trials
- ■ Bioethics training tips for IRBs
- ■ Using apps in research studies

CNE/CME QUESTIONS

1. Which of the following is a major issue for IRBs to consider when dealing with studies involving use of Internet and electronic social media?
   A. Possibility of re-identified data
   B. Fraudulent survey participation
   C. Security of data and privacy of mobile transmissions
   D. All of the above

2. Which state recently formed the first IRB collaboration between three Clinical and Translational Science Award (CTSA) institutions?
   A. Michigan
   B. Indiana
   C. Ohio
   D. Kentucky

3. Studies at Children's Hospital of Philadelphia that have gone through scientific review can go through the IRB approval process more quickly.
   A. True
   B. False

4. In the study by Zulman et al, what percentage of clinical trials reviewed excluded patients by age alone?
   A. 10%
   B. 20%
   C. 30%
   D. 40%

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