IRB ADVISOR

Your Practical Guide To Institutional Review Board Management

March 2013: Vol. 13, No. 3
Pages 25-36

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Do IRB members read protocol review folders before meetings?

Regulatory compliance is at risk

In days not so long ago, when all IRB members received heavy stacks of paper packets containing protocol submissions before each meeting, research institutions and regulatory compliance officials never questioned whether they would read the work before meetings. It was assumed they would be well-prepared for discussions.

Then technological change made it both possible and easy to find out if they actually do take a look at their packets prior to meetings. With submissions in electronic format, it's very easy to see if the electronic documents have been viewed.

And as a recent study shows, the answer can be surprising: At one institution, fewer than half of the documents IRB members were supposed to review were even opened electronically for viewing.[1]

Everyone, including the IRB members themselves, was surprised by the findings, says **Melissa Schlenker**, MS, CCRC, CIP, an IRB and clinical trials manager at WellSpan Health in York, PA.

Schlenker and **Tara Moore**, quality assessment specialist for research at WellSpan, published a study about their findings and quality improvement project to increase compliance at the Public Responsibility In Medicine and Research (PRIM&R) Advancing Ethical Research Conference, held Dec. 4-6, in San Diego.

When they discussed their paper with other PRIM&R attendees, they found that most of their IRB peers were startled by the study.

"We questioned whether we should take this [study] out to a national venue, but we felt like the benefits of identifying a problem and finding a way to correct it were important," Schlenker says. "Some of the comments at PRIM&R were, "I never thought about assessing whether our members are preparing for meetings.'"

From the IRB office's perspective, this was an IRB compliance issue that needed to be addressed and corrected, Schlenker says.

WellSpan Health's IRB members are volunteers who are

uncompensated for their time. Many have professional careers and may work for the organization in other full-time roles, so being an IRB member is a big time commitment, Schlenker notes.

"They're doing this on their administrative time, and we appreciate their commitment to doing that work," she adds.

IRB Advisor (ISSN 1535-2064) is published monthly by AHC Media, a division of Thompson Media Group LLC, 3525 Piedmont Road, Building Six, Suite 400, Atlanta, GA 30305. Telephone: (404) 262-7436. Website: www.ahcmedia.com. Periodicals Postage Paid at Atlanta, GA 30304 and at additional mailing offices.

POSTMASTER: Send address changes to IRB Advisor, P.O. Box 105109, Atlanta, GA 30348.

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Editorial Questions

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The IRB's membership mostly is stable, and members are well-trained, Schlenker and Moore say.

"I think we were very fortunate in the members we have on our board," Moore says.

There were some signs, however, that members sometimes attended the meetings with less than ideal preparation for the studies being discussed, Schlenker notes.

"Sometimes you'd get the impression from their questions that they didn't read the packets," she says. "We also had some trouble with IRB members' documentation, completing their reviews on time."

The IRB began to receive their submission and review packets electronically, and this change made it possible to check whether they were opening their packets prior to the meetings.

They found that out of five documents the members would receive, they'd open one or two, Schlenker says.

"We had a review checklist, and we tried to make sure the members came to the meeting prepared to have a meaningful discussion," she explains. "But when we saw the results, the light bulb came on."

They realized it was a compliance issue that could be addressed through a Lean Training methodology process and quality improvement project. *(See story on steps to improve compliance, p. 27.)*

Moore met with members of the IRB, thanked them for doing a good job, and asked if they had any concerns, suggestions, or comments. Since she is a long-time member of WellSpan's staff, the IRB members reacted without defensiveness when she discussed the report about their opening files.

"There was not one person who responded negatively," Moore recalls. "I received a lot of feedback from that."

The IRB members mostly wanted to know what they could do to improve their scores, Schlenker says.

"We had discussions with the IRB and said, 'Here are the things that need to be reviewed,' and we showed the list to them," she adds. "We had a discussion about what was preventing them from opening the file."

Chief issues included time and being too busy, not knowing which files needed to be reviewed most carefully, and even computer illiteracy, Moore says.

"Some people didn't realize they could scroll down to the bottom of the page," she explains.

"They just saw the cursor on the screen and thought that was it."

The quality improvement project has resulted in improvements in the quality of IRB discussions and in the percentage of documents opened, although the study's target goal of having 95% of the documents opened has not yet been reached.[1]

Most members now open 100% of their monthly review documents, but for a couple of people this has remained a challenge, Schlenker notes.

The change has also improved the IRB meetings qualitatively, she says.

"IRB members are better prepared for meetings," Schlenker says. "It's been a shared responsibility to improve the performance of our IRB members, make sure they have access to the tools they need, and it's been a positive experience for IRB staff and members."

REFERENCE

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Here are steps to improve IRB member compliance

Discuss issue with members

Research institutions with concerns about an IRB's preparation for reviews and regulatory compliance could learn a few lessons on how to assess their performance and improve any problems from the experience of the IRB at WellSpan Health in York, PA.

The WellSpan IRB discovered through a study of data from its electronic IRB submission database that IRB members were not reviewing all of the submission and review documents each month. This suggested the members were not well prepared for discussions and votes on board agenda items, which is a regulatory compliance issue. So the IRB began a quality improvement project, using the Lean Process and Methodology. It has resulted in improved training, better compliance, and more submission review files being opened each month.

Here's how the continuous quality improvement process works:

• **Assess compliance:** A couple of years ago, the WellSpan IRB began using and electronic IRB submission and review program that made it possible to identify whether IRB members were opening their review documents each month. A report generated by the software showed a high rate of noncompliance, says **Melissa Schlenker**, MS, CCRC, CIP, an IRB and clinical trials manager at WellSpan Health.

• **Learn more:** "We took the news to our director and IRB chair and vice chair and talked about it," Schlenker says. "We had discussions with the IRB."

They found that IRB members were very busy professionals, often running out of time to review a submission before the next IRB meeting and not knowing how best to prioritize the IRB review packet information they needed to read.

"Usually, they say they didn't have time — that's the biggest factor," says **Tara Moore**, quality assessment specialist for research at WellSpan.

In other cases, members had difficulty using the IRB electronic system with their electronic devices, such as iPads, for instance, Moore says.

"And we came to the conclusion that one thing that was not being taken into consideration is we have many different levels of computer literacy," she says.

"We received a lot of good suggestions, and we took the feedback to board members and said, 'Here's what we found out, so how can we help you fix the problem?'" Moore recalls. "By allowing them to give us feedback, we helped them become a solution to the problem, and we took everything into consideration."

• **Develop solutions:** Some monthly packages would have 20 files, but not all of these would require careful review, Schlenker says.

"We came up with one solution of simply flagging the items that most needed to be reviewed," Moore says. "That was an easy fix."

Also, Moore met individually with IRB members, at their request, to review their IRB material and help them go through the process of reviewing it. She taught them how to scroll down a page and move to the next items.

"I gave them individualized attention, which made them feel special and gave them assurance that they're doing it the right way," Moore says.

• **Continue tracking:** Each month, Schlenker checks data to see whether IRB members are opening their packets. "I run their numbers, checking their performance against what we expected them to open in the packet, and I give

that information to them," Schlenker says.

"We still have a couple of people who were maybe too busy, so they don't open the documents, and I'll go back to them and say, 'Hey, I noticed there was a problem, is there anything you need to tell us?'" Moore says.

Moore and Schlenker address any concerns the members raise.

"Over time, we have reached a certain level of compliance and have maintained that compliance over time, and that's been a good thing," Schlenker says.

• **Address limitations:** "The only caveat and limitation of the study was we could tell whether IRB members opened the document because the system tells us this, but we don't know how long they stay on each document," Schlenker says.

"We had very open discussions with IRB members about how we calculate data and graph it for them, but we can't tell how long they kept that document open."

An IRB member who wants to appear compliant could open each file, even if he or she didn't take time to read them.

"But we educated members on why it was important to open these specific documents because it would increase their knowledge," Schlenker explains. "And we addressed the regulatory component of approving or reapproving a project." ■

Data integrity should be top priority

Protect data to help protect subjects

As research institutions become more thoroughly electronic in their IRB and clinical trial systems, they should not lose sight of the importance of securing all transmitted data, an expert says.

"Institutions need to know what sites can do in collaboration with sponsors to promote data integrity through the life of data analysis," says **Michelle Stickler**, DEd, CIP, director of the office of research subjects protection at Virginia Commonwealth University in Richmond.

"The ultimate goal is to protect research participants, but at the same time we cannot produce new data without data integrity," Stickler says. "As we move to more use of electronic systems and electronic source documentation, there's going to be a greater need to think about who has access to these systems, is entering the data, and how we are making sure it's the person we think it is."

The trend toward electronic data suggests that research sites will one day be required by federal regulatory agencies to submit everything electronically, Stickler predicts.

"As we move to requirements to submit everything electronically, there's greater emphasis on collecting e-source documentation and data to get through the system and to pay more attention to the computer systems we're designing," she says.

Research institutions and IRBs also should know answers to these questions:

• How is information encrypted?

• Have secure transmission systems been established from site to sponsor?

• How can the institution verify if original information is put into the electronic source document?

• Which kind of system is being used to prevent problems from occurring?

The Food and Drug Administration (FDA) uses the acronym ALCOA as a guide for electronic-based and other evidence, and this is a good guide to use when assessing the integrity of an institution's electronic data system, Stickler suggests.

Using ALCOA as a guide, the data need to be:

• **Attributable:** Make data attributable to a source, and institutions should attribute data entry to a person or device or mechanism, Stickler says.

• **Legible:** Data have to be something the FDA can interpret, whether it's electronic or handwritten.

• **Contemporaneous:** If researchers include observation in their study, then data are entered in real time without a time lag in which some differences and inaccuracies could occur.

• **Original:** Research records should include the first, most accurate, and reliable recording of data.

• **Accurate:** Make sure what is being collected is, indeed, what actually occurred, Stickler says.

"We have to have secure systems," Stickler says.

While sponsors are responsible for much of this, sites also should maintain data security through knowing precisely who is responsible for creating data entered in the system, she adds.

"Whether it's a nurse coordinator or another person, everyone who enters data should have a unique identifier in the electronic system," she says. "If data are coming from electronic sources, like a blood pressure machine, then each piece of machinery needs to have its own unique identifier, and the site should maintain that list."

Sponsors also should maintain the list, and these two lists should be cross-checked when data are entered that are not on the list, Stickler says.

"You should make sure all information is from a reliable source," she explains. "This is part of a mechanism to make sure we're not getting tainted data and that we know where it's coming from, so we're not getting a random reading from someone who is not enrolled in the study, for example."

Another important component of ensuring data integrity is source verification.

"This is the responsibility of the site, as well as the sponsor," Stickler says. "The clinical research associate is the first line of attack for verification."

Institutions should ensure study participants meet all inclusion criteria and that records are capturing all of the medications subjects are taking and that lab results make sense, Stickler suggests.

"If one patient is making progress and then the next time is not doing very well, it needs to be checked out," she says.

The risk of having data inconsistencies and errors is that the FDA will not accept the data, she adds.

If this happens, it could lead to the sponsor failing to have adequate data to support claims about a new product, and the site might be blackballed by sponsors due to its poor data integrity, Stickler says.

From a human research protection perspective, this means the time subjects spent participating in the study was wasted, and it may leave them unwilling to participate in future research.

"Potentially, we may have increased risk to research participants for very little value in the end," Stickler says.

Data storage is another big data integrity issue.

"I've been reading about some potential issues with data storage when everything is electronic," Stickler says. "While we think it's safe and long lasting, and we think we can hold everything electronically, there are papers out saying when you go back to retrieve data there could be some chunks missing."

Research sites must maintain data for at least two years after the product is evaluated, so they may need to re-evaluate their data storage system to make sure it can handle data for the length of time necessary and test it for long-term integrity issues.

"This is an issue for IRBs, sites, and medical centers," Stickler says. "Do they have adequate data capacity and retention systems to maintain data electronically for that long?"

The standards suggest having a minimum of two back-up storage locations, she notes.

"Here, we're looking at a double back-up system with servers here at this institution and another back-up that is within our general region, our city area," she explains. "A second back up is in a completely different country."

The reason for the remote back-up is that if a region is struck by a natural disaster, the data stored locally could be affected.

"You want it in a different weather region," Stickler says.

An example would be when Hurricane Katrina hit New Orleans and caused massive destruction, interrupting clinical trials and annihilating data that was stored locally in flooded buildings.

"In a situation like New Orleans, the data could be gone with nothing to reconstruct," she adds. "All research subjects have gone through the study, and it's all been for naught."

Another aspect to data integrity involves custody documentation and the audit trail.

Research institutions should look at making these two chief improvements, Stickler suggests:

1. **Limit access:** Limit access to audited users. This keeps data accountable.
2. **Use common sense:** "When a programmer leaves a station, log off so data are not sitting there on the screen," Stickler says. "If a system is idle for five minutes or more, it should be automatically logged off, locking the computer."

These are small actions that most institutions may not have on their radar, but implementing those actions in the research and IRB workplace could improve data integrity.

"In terms of the audit trail, we look at keeping track of all the changes made to the paper trail, providing explanations of any changes, and the same is true of the electronic trail," Stickler explains. "Find out when a change is made, who is making the change and have them log in and capture unique information, tying it to the change so it can help us create an audit trail."

Anyone who changes or adds to electronic data

must be required to log in so their input can be captured and traced back to them.

"I think the key to data integrity is being able to tell a story from start to finish so we have all the details, including where data came from and being able to double-check data to verify the data's quality," Stickler says. ■

Therapeutic misconception not well understood

Put subjects' comments into context

What IRBs and the research ethics community commonly believe is evidence of therapeutic misconception among research participants often is the result of misinterpretation by the experts, a researcher says.

A new study that looks at therapeutic misconception found that most individuals who enroll in a clinical trial have a desire for a therapeutic benefit, especially when there are no other treatment alternatives, but this motivation does not prevent them from fully understanding randomization.[1]

"What we found was that pretty much people understood and appreciate the randomization probabilities," says **Scott Y. Kim**, MD, PhD, an associate professor in the department of psychiatry and co-director of the Center for Bioethics and Social Sciences in Medicine at the University of Michigan in Ann Arbor.

Kim was the principal author of a study that looked at how individuals made decisions about whether to enroll in a Parkinson's disease clinical trial that involved randomization to a gene-transfer arm or a sham surgery arm.[1]

Participants of the trial received surgery to their heads for a gene transfer if they were in the intervention arm. The sham arm participants had a hole drilled in their heads, but nothing was implanted in their brains, Kim explains.

Investigators asked participants: "What are the chances of a participant being assigned to the sham surgery group [or gene transfer group]?" They designed this question be in the third person to ascertain their intellectual comprehension of randomization ratios. The randomization ratio for this trial was one to one, so a correct answer would be 50%.[1]

A second question they asked participants was similar but more personal, to see if they could apply the information to themselves: "What do you think your chances are of being assigned to sham surgery [or gene transfer group]?"[1]

For the first question, 83% of respondents said there was a 50% chance of assignment to either arm. For the second question, 55% gave the correct quantitative answer as well as making a variety of comments, while the remainder only made various qualitative comments. The comments were similar in two groups, and at first appeared to show a misconception, such as "I'd be disappointed if I don't get the real thing." But Kim and co-researchers noticed that people who clearly both understood and applied the randomization probabilities to themselves also made the same types of concerning comments.[1]

As they analyzed these comments, it became apparent that participants were communicating something other than their knowledge of randomization probabilities, Kim says.

"They made a lot of comments that if taken in isolation would have suggested they didn't know what was going on," he explains. "They seemed to be saying, 'I'll be surprised if I don't get the real thing — meaning the gene transfer intervention.' The person may say that but have correctly answered everything to that point. How do you interpret that?"

But then, they would talk about how many people are praying for them, or their hope that positive thinking will make a difference, or even express their belief in "luck," Kim notes.

Taking the context into consideration, IRBs and bioethicists might look at this apparent incongruity as being similar to what happens when people identify with a particular sports team, Kim suggests.

One's team might have a losing record this season and be slated to play on Saturday against a team with a no-loss record. Objectively, most people would predict the opposing team to come out victorious, but the person who favors the hometown team might reframe the match-up, saying there was a good chance their team might pull an upset, he explains.

"In terms of probability, this makes no sense, but the person is obeying the rules of a sports conversation," Kim adds. "If we understand the context in which they're making these statements it might be quite rational."

The concept Kim and co-researchers believe IRBs and bioethicists need to pay more attention

to is the notion of pragmatics in linguistics: "How people communicate and convey meaning by the context — not just by the semantic meaning of words," Kim says. "It's like when someone asks, 'Can you pass the salt?' We all understand what they mean by the context."

When evaluating the quality of informed consent in a study, IRBs and researchers might consider the context.

"If you violate the norms of conversation, you will create confusion — for example, providing excessive reassurances in a study with minimal risk," Kim says. "It is a problem because IRBs are so used to requiring it they accept it as a conventional way of doing things. But it's not conventional for the subjects."

The study's conclusion is that most people who have serious illnesses and enter a clinical research trial do have a therapeutic motivation, meaning they hope to benefit from being in research and will focus on that motivation because for them, that is what is on their minds, he adds.

"But this doesn't mean they do not know what they're getting into," Kim says.

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1. Kim SYH, de Vries R, Wilson R, et al. Research participants' "irrational" expectations: common or commonly mismeasured? *IRB: Ethics & Hum Res*. 2013;Jan-Feb:1-9 [e-pub: http://www.thehastingscenter.org/Publications/IRB/Detail.aspx?id=6189.] ■

IRB takes data storage to the cloud

Accessibility advantages to using cloud storage

IRBs run on data and paper — and lots of it. Some organizations may find themselves running out of space to store the reams of paper that are needed to catalog the scores of research and submission data. This has led some IRBs to look for alternative methods of data storage. But an IRB can't live without paper — or can it?

To solve this problem, some IRBs have turned to electronic systems and cloud storage. "The cloud" refers to an off-site place, usually the Web, where data is stored. There are no in-house servers or computer systems used for the storage. Examples of cloud storage include Web-based email programs, online document sharing programs, or sites from where users can stream videos. Basically, "it's just a big spot to store stuff," says **Walden Leverich**, CEO of Tech Software in Melville, NY. The non-cloud alternative, he says, is in-house installed servers and desktop systems.

With cloud storage, researchers can easily move files between people. Everyone involved with the IRB or a particular study can access the data remotely without having to worry about being blocked by the institutional firewall. And, as Leverich points out, getting IRB and research data access for anyone outside of the institution can practically take an act of Congress to get approved.

"There are a lot of things they don't want outside people to get at," he says. The issue, though, is that IRB members and researchers may do a lot of after-hours work from home and may have difficulty getting behind the firewall. "Hosting a cloud-based solution, they can get into it with their password," he says.

"The beauty of having the databases is we can access them from anywhere," says **Kimberly Irvine**, CIP, CIM, executive vice president and chief operating officer of Biomedical Research Association of New York (BRANY). "It makes it a lot easier to make information available to a wide variety of people and makes the information available at a variety of locations."

BRANY has been using cloud databases since 2000. Instead of uploading everything to the database all at once, the IRB slowly phased it in until all the documents were electronic. IRB members received one-on-one training and webinars to learn the system. Once everyone got used to it, the IRB expanded to using electronic submission forms for researchers.

"IRB members are able to access information from anywhere with the right permissions," Irvine says. "There's so much more flexibility in the process — people don't have to sit in a room and fumble through the paper. When we first started expanding to electronic databases, we had the naysayers who said they still needed their binders and paper and were skeptical, but now they are amazed of all they can do with the workflow available. That's been kind of interesting to witness."

There is also an infrastructure advantage: All that's needed to access the cloud is an Internet connection and a browser. "There's no software, no need to wonder whether it's set up on certain

machines," Leverich says. "The IRB doesn't have to worry about data backups being done, or about maintaining servers involved — that's all on the cloud provider."

Keeping everything secure

Certainly one of the biggest questions when considering a cloud system is security. Will sensitive research participant data be kept safe? Keeping the data secure is not just up to the cloud provider — IRB members must also do their part to keep information safe.

"Our job is to make sure things stay secure and compliant, though it stays compliant to the degree we can keep it compliant," Leverich says. "The in-house user community is still using the system. If the in-house staff doesn't do their job in security, we can't do ours."

For example, "If you're a user and you log into that system at Starbucks and you walk away and leave the screen up, that's a big security risk," he says.

Part of keeping data secure in the cloud system is to educate IRB members on their roll in the process. "You have to educate the users to know that they're not supposed to share passwords and access with others," says **Raffaela Hart**, BS, CIP, CIM,vice president of IRB and IBC Services at BRANY. "They have to help maintain security. Sometimes submissions have information related to the research visits, and that could contain info that may be identifiable. We have to worry about that, too."

"It brings a new set of concerns because third-party providers are now sort of mediating the relationship between researcher and subject," says **Michael Zimmer**, PhD, assistant professor and director of the Center for Information Policy Research at University of Wisconsin-Milwaukee. For example, if a researcher is using Facebook sidebar ads to recruit subject for a study on drug use, Facebook would know if a person clicked on that particular ad. The concern that arises is whether Facebook would then collect and use that data for other purposes, such as marketing. "That takes extra work to be concerned about what Facebook knows about the research subject — do we need to be worried about Facebook collecting data? The challenges with cloud services is that it presents all these issues IRBs may not have thought about before," Zimmer says.

"A lot of times the concerns make sense — the level runs the gamut from 'I'm not worried about it' to 'It's a big, important thing for the contract.' Different IRBs have different needs — it's the nature of local context like everything else," Leverich says. "Community needs and risks are different. All IRBs have different acceptable risks for the cloud component."

Making the switch?

Here are a few points for IRBs to consider when thinking of switching to a cloud-based system:

- Before you do anything, vet potential cloud vendors. Be sure to perform due diligence into a company's practices, security, and facilities before deciding to make the switch. "Find out where the vendor secures their data, what server facility they're using, if they have the right security and backup procedures in place — those were things we took into consideration when vetting the vendor," Irvine says "We looked at where they were housed and where they would be in proximity to us."
- Have a plan in place when switching from a paper-based system to an electronic interface. "It's going to be a transition for researchers and reviewers who are used to a paper system," Leverich says. "You're going to have to have a process in place for dealing with that transition." And when moving to electronic processes, some IRBs take the opportunity to reconfigure work flow and submission forms. "Make sure you have a plan in place before choosing a new solution, or work with your solution provider to develop one early on," he says.
- Consider whether you want a fully paperless system, or want the system to mirror the paperwork. "It all really relates to your IRB process. If you meet in a room all the time, maybe it's worthwhile to have paper or have documents in front of you," Hart says.
- Think about how the IRB's standard operating procedures (SOPs) could be affected. For example, going paperless may mean documents will no longer require a hand signature, though signature requirements may be listed in the SOP. "What do you do if you don't have a signed document?" Irvine says. "If you're moving to something paperless, then all your SOPs need to be changed to not require signatures anymore. Think of all the things that lead up to having documents signed and what you have to modify. We were recently working through that and didn't realize how many times we talked in the SOPs about signing documents."

• Who will own the data? If the cloud system is managed by a third party, there may be some concern from IRB members and researchers about whether the management company will own the data — or, worse yet, share or sell the data to other companies. "You want to make sure when you're choosing cloud services that it's clear you're not giving the service your data," Zimmer says. "You'll want to know if there's anything in the contract about whether to share the data with anyone. I would suspect they would all say they don't, but you want to validate."

Some things to clarify with cloud management services, Leverich says, include: How will you get your data out if you decide to switch providers? Are you the only person using that data, or can the cloud provider aggregate that data and do things with it? What's the stewardship of that data, and what are the restrictions? What are the tracking and auditing capabilities in the system for changing data?

The risks of data sharing, Zimmer says, are almost non-existent. "Most of the contracts protect against these things, and most companies would go out of business if they were selling the data," he says.

Zimmer also suggests considering what kind of encryption a cloud system has, and whether a clinical trial participant's IP address can be logged in a way to allow re-identification. ■

GlaxoSmithKline to begin publishing trial data

Drugmaker GlaxoSmithKline (GSK) has announced its intentions to start publishing clinical study reports (CSRs) and clinical trial results in an effort for increased transparency, making it the first major drug company to do so.

GSK will begin publishing CSRs for all drugs once they have been approved or discontinued from development and the results have been published, the company said in a statement. Researchers and regulators would have first review of the data, with identifying patient data removed to ensure confidentiality.

The move comes in the wake of a $3 billion settlement GSK paid out in July 2012 after admitting to charges of manipulating trial data, hiding unflattering scientific studies, and enticing physicians to prescribe the antidepressant Paxil. The company admitted to covering up studies and other evidence that showed Paxil caused harmful side effects in children, including suicidal ideation.

GSK announced it would develop a system where researchers will be able request access to detailed anonymous patient-level data that sit behind the results of clinical trials to enable additional scientific inquiry and analyses to help further scientific knowledge. The company stated that the initiative is part of a commitment to greater clinical trial transparency.

In addition, GSK will have teams working on publishing all CSRs and trial data dating back to the company's formation in 2000, when Glaxo Wellcome merged with SmithKline Beecham. "Given the significant volume of studies involved, the company will put in place a dedicated team to conduct this work which it expects to complete over a number of years," the statement said. "Posting will take place in a step-wise manner, with priority given to CSRs for its most commonly prescribed medicines."

The company already publishes some clinical trial data online at http://www.gsk-clinicalstudyregister.com/, with summary information on about 5,000 clinical trials. GSK will also look to publish evaluations of its medicines in peer-reviewed journals.

"We are committed to being transparent with our clinical trial data to help advance scientific understanding and inform medical judgment. Our commitment also acknowledges the very great contribution made by the individuals who participate in clinical research," says Patrick Vallance, President, Pharmaceuticals R&D, GlaxoSmithKline. "All those involved in the conduct and publication of clinical research, whether healthcare companies like GSK, academia or research organizations, have a role to play in ensuring that the data they generate are made publicly available to help bring patient benefit." ■

FDA lays path for early Alzheimer's trials

The Food and Drug Administration's Center for Drug Evaluation and Research (FDA CDER) has issued a draft guidance to make it easier for development and testing of Alzheimer's treatments

in patients at an early stage of the disease. This may pave the way for researchers to develop trials for patients before they develop overt dementia symptoms.

"Specifically, this guidance addresses the FDA's current thinking regarding the selection of patients with early AD [Alzheimer's disease], or patients who are determined to be at risk for developing AD, for enrollment into clinical trials," the draft guidance states.

"We recognize that the standard approaches to the selection of outcome measures historically used in the development of treatments for dementia of the Alzheimer's type have major limitations when applied to clinical trials enrolling patients in the early clinical stages of the disease, or before clinical impairment has emerged at all," the document continues. "This guidance addresses some possible adaptations of the current approach to drug development for the treatment of the dementia stage of AD that appear more appropriate for clinical trials in the early stages of the illness."

The guidance will help researchers develop trials for very early signs of Alzheimer's disease, such as Alzheimer's-precursor prodromal disease. Drug development has become more focused on these early stages, the FDA says, because disease-modifying therapy is thought to be of greater benefit then, though no drugs have yet shown to be effective in that area.

Indeed, development of disease-modifying treatments for early-stage Alzheimer's have recently fallen short. Johnson & Johnson, along with partners Pfizer and Elan, ended trials of potential disease-altering drug bapineuzumab after clinical trials failed to show any benefit in patients. Eli Lilly's solanezumab was also determined to be ineffective in patients with more advanced forms of the disease, though it was recently selected for trials in patients at risk for the disease, but not yet presenting symptoms.

"The scientific community and the FDA believe that it is critical to identify and study patients with very early Alzheimer's disease before there is too much irreversible injury to the brain," Russell Katz, MD, director of the Division of Neurology Products in the FDA's Center for Drug Evaluation and Research, said in a statement. "It is in this population that most researchers believe that new drugs have the best chance of providing meaningful benefit to patients."

For drugs designed to treat patients with overt dementia, the FDA currently requires that treatments not only show an effect on abnormal thinking, but also how well patients function. The goal for these trials is to ensure that any beneficial effect on thinking is associated with a clinically meaningful outcome for the patient. The agency also stated that it is open to considering positive biomarkers as a secondary outcome in combination with a positive primary outcome.

"Guidance for Industry, Alzheimer's Disease: Developing Drugs for the Treatment of Early Stage Disease" can be found at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM338287.pdf. ■

Study identifies barriers to use of central IRBs

A study conducted by the Clinical Trials Transformation Initiative (CTTI) identified some of the barriers IRBs may face when choosing a central IRB for multicenter studies. "Using Central IRBs for Multicenter Clinical Trials in the United States," published in the journal *PLOS ONE*, gives recommendations for IRBs to overcome the barriers to choosing a central IRB and improve the efficiency of multicenter studies. CTTI is a public-private partnership established by Duke University and the Food and Drug Administration that comprises more than 60 member organizations to improve the quality and efficiency of clinical research.

The CTTI researchers conducted a literature review and interviewed IRB representatives from institutional IRBs, federal IRBs, commercial IRBs, industry, and regulatory agencies. "Our goal was to identify the range of perceptions and beliefs among diverse participants, and not to establish the prevalence of different views," the study authors wrote.[1]

"To help with this, we developed a guide to support communication between a research institution and a central IRB as they develop an agreement about who will do what for a given trial," says the study's lead author, **Kathryn Flynn**, Ph.D., assistant professor of medicine at Medical College of Wisconsin. "We hope sponsors in a position to do so require the use of central IRB review for multisite trials, to allow stakeholders to gain experience that may foster greater comfort and trust with that model."

Barriers the authors identified include:

• The feasibility of working with multiple outside IRBs, each having its own protocol submission process.

• loss of revenue generated from fees for review of commercial-sponsored studies;

• concern for noncompliance and regulatory liability;

• concern for legal liability in the event of litigation secondary to errors, omissions, or negligence of an IRB not directly affiliated with the IRB conducting research;

• quality of review;

• potential loss of local context (for example, unique patient populations, local knowledge of investigators, or a center's resources for conducting the research).[1]

The authors of the study developed a list of solutions for the identified barriers, including establishing liability protections, clarifying policy to take action against the IRB of record in the case of noncompliance, conducting standardized quality tests of IRBs, and developing a detailed communication guide with information on the study site, investigators, and other local data.

The study also uncovered confusion over the responsibilities of institutions and central IRBs.

"A major finding was that many of the perceived barriers to using central IRBs arise from the fact that most or all of the tasks related to protecting the institution (e.g., conflict of interest review) are often coordinated through the institution's IRB office and incorporated into their review process," the study authors wrote. "What evolved as bureaucratic convenience in most institutions — locating certain institutional review processes in the IRB office — seems to have altered perceptions of what is entailed in the ethical review of research. This conflating of institutional responsibilities with the ethical review responsibilities of the IRB leads to confusion about how institutional responsibilities would be handled in the context of a central IRB review, creating resistance to using central IRBs."[1]

To address the problem, the authors developed a guide to assist IRBs in breaking down which responsibilities go to the central IRB, individual institutions, or both.

"The clinical trials community has an opportunity to significantly improve the quality and efficiency of one essential aspect of the clinical research enterprise, as there is good reason to believe that central IRB review would be beneficial to clinical research," the authors stated.[1]

REFERENCE

1. Flynn KE, Hahn CL, Kramer JM, Check DK, Dombeck CB, et al. (2013) Using Central IRBs for Multicenter Clinical Trials in the United States. PLoS ONE 8(1): e54999. doi:10.1371/journal.pone.0054999 ■

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

■ Institution overhauled its IRB review process, improving quality, efficiency

■ Community-based research can raise some issues for IRBs

■ IRBs can help PIs make better IC forms through "Consent Builder"

■ Whole genome sequencing in pediatric research

CNE/CME QUESTIONS

1. When one institution studied IRB members' regulatory compliance by reviewing electronic data on how many IRB protocol submission documents they opened prior to the monthly review meetings, what did they find?
   a. 90% of members opened 100% of the documents.
   b. All but a few members were 100% compliant.
   c. Fewer than half of the documents members were supposed to review were not opened.
   d. Only 42% of IRB members were compliant.

2. The ALCOA rule about ensuring data integrity is an acronym for which of the following:
   a. Attest, lawful, confirm, order, authenticate
   b. Attributable, legible, contemporaneous, original, accurate
   c. Actual, line-by-line, causal, original, accurate
   d. Attributable, logical, corrected, only one, appropriate

3. According to a recent bioethics paper on therapeutic misconception, researchers need to pay more attention to the notion of pragmatics in linguistics because how people communicate their understanding and desire regarding enrollment in a study with randomization could be an indication of their type of communication in that context and not an indication that they do not understand their true odds for being enrolled in a study's therapeutic arm.
   a. True
   b. False

4. Which of the following are issues to consider when switching to cloud-based IRB data storage?
   A. Who will own the data.
   B. What the tracking and auditing capabilities are.
   C. The company's security and backup systems.
   D. All of the above.

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