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Put 'metrics' in the lexicon after IRB, before quality improvement

Metrics are key to use of e-data

It is a natural electronic data evolution: First, IRBs began using electronic data systems; then these morphed into full electronic submission, and now IRBs are collecting valuable electronic, real-time data that can be mined very quickly for process and quality improvement purposes. Metrics are key to this transition.

"It seemed intuitive to me," says **Daniel Nelson**, MSc, CIP, director of the office of human research ethics and professor of social medicine and pediatrics at the University of North Carolina at Chapel Hill. Nelson spoke about using metrics to monitor, manage and improve IRB operations at the recent Advancing Ethical Research Conference of the Public Responsibility in Medicine and Research (PRIM&R), held Dec. 4-6, 2012 in San Diego. Nelson has been using metrics since before most IRBs collected all data electronically. *(See story about how to implement a metrics system, page 15.)*

"When I moved to UNC 15 years ago, one of the first things I did was look through stacks of paper and data," Nelson says. "With a scientific background it was second nature to analyze and track things."

At first, collecting metrics was a paper-based, often tedious process of sifting through paper records. Now it's a matter of running reports and analyses electronically.

"We do this at the end of the calendar year with some reports at the end of the fiscal year," Nelson says. "The time frame varies, depending on how people run their operations."

The UNC IRB collects metrics for routine, ongoing tracking, as well as for tackling specific performance improvement issues, he adds.

Metrics also are being used by IRBs for benchmarking purposes.

"The important thing for any IRB is to have some method to measure indicators of quality, first, and then to act on them," says **David G. Forster**, JD, MA, CIP, chief compliance officer at the Western Institutional Review Board in Olympia, WA. Forster spoke about

collecting and analyzing metrics for quality improvement at the PRIM&R conference in December 2012.

Electronic data has made collecting metrics far easier, he notes.

"Back in the old days of paper-based IRBs, it was hard to measure much," he says. "You had to record it somewhere to figure out what you had to work with."

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Editorial Questions

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Quality improvement efforts at IRBs have taken a giant step forward with the transition from paper to electronic data over the past 15 years, Forster says. "We have an incredible ability to increase measuring what we do," he adds. "There's been a gradual process to electronic data; in 1995, WIRB had a rudimentary system that tracked what we had to find in a paper file. In 2002, we switched to a completely electronic system."

At UNC Chapel Hill, a fully integrated electronic data collection process has been in place relatively recently, Nelson says.

"We put a home-grown application system in effect in 2011," he says. "We did it in a phased-in approach, rolling it out with the behavioral and social sciences departments first and then with the biomedical departments."

The IRB tracked information all along and learned from the data metrics.

For instance, it discovered that IRB processing times actually increased by 300% when the electronic transition took place, Nelson says.

"Our processing times went from a couple of days to a couple of weeks," he says. "It was a lot longer, which is why I realized we needed to do something because we had implemented a system that was supposed to make things easier for the staff and IRB, and, instead, things got much more complicated and slower."

At first, this trend was observed by investigators and research staff who complained that response rates had slowed down. A metrics analysis confirmed their anecdotal evidence. The next step was determining what caused the negative change and correcting it.

"We analyzed what people were doing, how they were doing it, and how the system could be improved," Nelson says. "We used an all-systems approach to handle the backlog snowballing on us; we made changes and adjustments that were able to bring down our turnaround time for expedited review."

Changes included adjusting staffing positions to put more employees in the roles that needed more attention under an electronic system and decreasing staff from areas that needed less staff with online IRB submissions, Nelson explains.

The expedited review time, which had skyrocketed to 18 days from three days, was brought down to three days initially. Now it takes one or two days and is tracked on a quarterly basis, Nelson says.

In WIRB's more than 10 years of experience

with electronic data and metrics, the focus has gone from what to measure to how to measure, Forster notes.

"The first look by everyone is in turnaround time," he explains. "But the devil is in the details: How do you measure it? Do you review the complete system, measuring it from when the application goes to the board or staff, or when they work on it after the board meets?"

Once an IRB sets up its measurement parameters it can determine what is working and what is not and what the trend is. While collecting and comparing data is easier, the challenge continues to be in the analysis.

For instance, metrics might show that an IRB's submission packets were taking three days but now are taking five days.

"What is the cause of that? You can get a very detailed look at your processes," Forster says. "You need to divide up each type of work and then track it."

Forster and Nelson outline these strategies IRBs can use to improve to track and analyze metrics:

• **Select initial areas to track and trend.** Most IRBs begin with tracking the time it takes to complete an IRB review. They can select beginning and endpoints, such as starting with the date the submission was received by the IRB until the date it is sent back to the investigator with an approval or request for more information, Nelson suggests.

Other activities that might be selected for collecting and tracking metrics include these:

- total submissions;
- number of exemptions;
- how many submissions are screened and then returned as not requiring further review;
- staffing levels;
- number of unanticipated problems.

"Once you measure something you can make changes as part of a continuing quality improvement cycle," Forster says."For example, if you realize the timeline for processing unanticipated problems is three days, then you look at why it takes three days; once you measure it, you can improve it."

• **Measure error rates**. IRBs can use metrics to identify errors in electronically submitted documents, including consent forms, Forster suggests.

Using metrics, IRBs can identify trends that point to certain areas of a form that cause the most errors or problems.

"You can use that information to do some real quality work of looking at root cause problems," Forster says. "If you see a trend toward spelling errors in the consent form, you can measure this and find out why we're making spelling errors."

• **Assess the relationship between staffing level and workload**. IRBs can use metrics to make certain the staffing level can handle the current workload on an ongoing basis.

"If the workload is outpacing staffing, we make adjustments to create new positions," Nelson says.

"We look at where our research is coming from, which department is contributing the most research," he adds. "Every department thinks their research is the most important research, and sometimes it's an eye-opener for them to realize they were only 5% of your research portfolio when they thought they were closer to 100%."

Trends in workload shifting don't occur that fast, Nelson notes.

"There may be a shift on a month-by-month basis or a spike when students come back to school," he notes. "But it doesn't change the overall workload of the office." ■

Expert tips for improving metrics systems

Design systems for best measurement

When an IRB initiates electronic metrics collection and analyses as part of its quality improvement process, there will be obstacles to overcome. However, there are ways to make the transition smoother, including investing in designing the electronic system to obtain the measurements that will be the most useful, experts suggest.

"It often occurs that you decide to focus on a particular issue and you realize you didn't design the system in a way that you can measure that issue," says **David G. Forster**, JD, MA, CIP, chief compliance officer in the office of compliance at the Western Institutional Review Board in Olympia, WA.

"That's a constant — developing new searches," Forster says. "Programmers come up with new searches we didn't think of in the original build."

For instance, a routine data collection that

IRBs should anticipate involves workload and its relation to staff and IRB meetings, says **Daniel Nelson**, MSc, CIP, director of the office of human research ethics and professor of social medicine and pediatrics at the University of North Carolina at Chapel Hill.

"How does the workload relate to the length of the IRB meetings?" Nelson says. "Some of these [measures] are done on a routine, ongoing basis with no real specific problem or issue we're trying to address."

Forster and Nelson offer these additional suggestions on how to best use IRB electronic metrics to make the transition to paperless data collection and analysis smoother:

• **Anticipate an adjustment among IRB staff and investigators.** "That's predictable," Nelson says. "We did inservice training and had campus-wide training systems."

Even with training and plenty of time to prepare staff for the change, problems can occur. The UNC Chapel Hill IRB experienced the increased processing time, and this meant something was not working as well as expected.

"We needed to recalibrate some of our expectations," Nelson says. "One of the reasons for having metrics and monitoring them on an ongoing basis is you have new employees and turnover, and it doesn't take much to find that what was expected and normal for one group of employees may not be normal for a new group of employees; it's not all about turnaround time."

• **Make certain your electronic system is compliant with regulations.** "This is time consuming and expensive, but good to do," Forster says. "If you are an IRB doing FDA-regulated research, it's a good practice to have your system compliant with 21CFR, part 11 rules on electronic recordkeeping and signatures."

To meet the requirements of part 11, IRBs have to validate your system, write test scripts for everything the system is supposed to do, and to test it to see if it actually does it, he explains.

"This makes your system more reliable and is a good practice for developing information technology systems," Forster adds. "While the FDA is not proactively applying it to IRBs, it is in the manual that FDA uses to guide itself on FDA inspections, and it does include part 11 as one of the issues."

• **Test and validate the system.** When an electronic system is designed or revised, there will need to be tests and validation.

"You have to come up with a list of user requirements and for every user requirement, every function your system does, you have to write a test," Forster says.

"If you enter an investigator's name and push this button, it should populate a field, and then you can run a test and say, 'Yes, it did this,'" he adds. "It's very time-consuming."

But this level of validation is necessary to ensure accuracy in the electronic records, and accuracy is essential for compliance with federal regulations, Forster says.

It's also important to train the electronic system's users on how to enter data and to make sure the system is user friendly, Forster notes.

"We have quality checks we run," he says. "For instance, we make sure we didn't miss any continuing review anniversary dates, and we run that check once a week." ■

BEST PRACTICES SPOTLIGHT

Focus on what your IRB client wants

Submission forms need reworking

IRBs and human research protection staff engage in important, sometimes life-protecting work. Their purpose and goals are on high ethical and moral ground. So it's easy to forget that it's also an enterprise with clients or customers to satisfy.

"Over the past few years, we've really been focused on listening to the voice of the customer: the research community, investigators," says **James Riddle**, MCSE, CNE, CIP, assistant director at the institutional review office at Fred Hutchinson Cancer Research Center in Seattle.

"We now ask: 'What can we do to help you get your research done more easily and faster?'" he says.

The point is that IRBs can improve their research review quality and improve their client satisfaction by focusing on how they and their forms communicate with researchers.

"The primary thing we learned was that most

IRBs — and ours was no exception — write their forms to help them keep their records, stay in compliance, and to reflect the perspective of the regulator," Riddle says. "What we were missing was the utilization of the forms by the end user and how they might choose to interact with the forms."

The organization hired an expert who has a master's degree in linguistics and a master's of science degree in human-centered design and engineering to help the IRB design data structures that would result in the most accurate data while being user friendly, Riddle says.

"She was invaluable," he says. "Her advice to us was to create forms that have a thoughtful progression of the information."

At the expert's suggestion, the IRB now has a trained IRB professional create forms using four guiding principles, Riddle notes. The principles are as follows:

1. Write clearly and plainly.

"They should be understandable to a reader with some level of familiarity with research and regulations, but who is not a regulatory expert," Riddle says.

IRBs now are paying more attention to the wording in informed consent forms, and they should apply some of the same strategies to making their submission forms more readable and simple, as well, he adds.

"Make sure the forms are focused on your customer," Riddle says.

Here are some question examples from the IRB's new submission form:

"Is there a separate research protocol, synopsis, or other document detailing the study's research procedures?

- "Yes – please submit protocol
- "No – please describe research plan in detail:"

Another plainly worded question on the new form is this: "How long will individual participants be in the study, and how long do you expect the entire study will take to complete?"

2. Target questions to the expected user.

One form does not fit all, Riddle says.

"Don't ask questions the end user doesn't need to complete," he advises. "Ask only questions that pertain to the user completing the form and that user's particular kind of research."

For example, a Fred Hutchinson researcher who is doing epidemiological research about prostate cancer biomarkers does not need to answer questions about investigational drug research or experimental devices, Riddle explains.

"What we found was our forms were so regulatory-focused that they asked the same questions of everybody," he says. "Everyone had to answer questions about devices, whether they were using them or not. That meant users had to read and decipher and understand a question they never needed to answer in the first place."

Even when IRB forms are electronic and contain decision trees, allowing users to skip a question if they answered the previous question a certain way, researchers can find this confusing, Riddle says.

"We found users were even getting confused by questions that allowed them to skip other questions," he explains. "By having more targeted forms, we were able to eliminate a number of those decision points so the end user will not have to waste time on this."

3. Do not duplicate questions on forms.

"Do not ask the same question twice, and don't require duplicate data," Riddle says.

Prior to Fred Hutchinson IRB's quality improvement project, all IRB forms asked researchers to record inclusion and exclusion criteria for the research protocol on the form, he notes.

"We had them enter those data in the form although the data exists in a separate research protocol," he explains. "So they'd cut and paste it into the IRB form."

Forcing users to duplicate data can introduce errors unnecessarily, he says.

The solution is for the IRB to go to the source data for this information.

"We found it was more effective to ask in the IRB form, 'Where is this data in the protocol?'" Riddle says. "That eliminated a lot of error and it eliminated a lot of angst from the users."

For example, the IRB's new submission form has a question, stating: "What are the objectives that will be met? If this information is clearly described in the protocol, reference the specific page(s) where applicable:"

4. Create forms that can be audited.

"The forms had to be auditable — that's the term we came up with," Riddle says. "What that means is the forms must provide the researchers, the IRB, and the center/institution overall with some means to transfer information

from the principal investigator to the IRB in a way that is compliant and auditable by federal regulatory agencies."

Forms can be simplified but not eliminated entirely. Also, all IRB communications with researchers need to be documented so an auditor can see what has occurred, he adds.

"We came to the conclusion that you could not have some sort of unstructured, unfettered communication," Riddle says. "You have to have a form at some level."

Regulators look for forms with signatures on the page, documents they can review, he adds.

Since re-engineering the IRB's application process and forms, there has been a 20% reduction in errors, researchers report spending less time completing the forms, and IRB staff spend less time reviewing the forms, Riddle says.

"And the forms are more accurately filled out," he adds. ■

True simplicity remains elusive for IC forms

Readability improves, length increases

Informed consent documents remain long and complex, despite successful efforts in recent years to improve their readability, an expert reports.

"Our IRB at Johns Hopkins University was often trying to make consent forms shorter and simpler, recognizing that this tends to make it easier for the participants to understand," says **Nancy E. Kass**, ScD, deputy director of the Berman Institute of Bioethics and Phoebe R. Berman Professor of Bioethics and Public Health at Johns Hopkins University in Baltimore.

Unfortunately, the IRB ran into roadblocks in the form of multicenter studies where the IC form was drafted centrally and could not be shortened by the IRB, she notes.

"Our IRB was frustrated by this, so I decided to look into it further," Kass adds.

The IRB worked with a contact at the National Institutes of Allergy & Infectious Diseases (NIAIDs) of the National Institutes of Health (NIH) to review all informed consent forms used in HIV study networks. The consent forms reviewed came from studies that were conducted across the world, she says.

"We asked only for the HIV networks," Kass says. "We found good news and bad news: The good news is that compared to studies done 10 to 20 years ago, the readability of consent forms as measured by the Flesch-Kincaid readability score was at a 9.2 grade level."

Studies of IC readability from 10 to 20 years ago found that consent forms were written at graduate school level, so the 9.2 grade level average was an improvement, she adds.

"Also, the choice of words and sentences were simpler than what they were 20 years ago, and that's the good news," Kass explains. "There have been a lot of messages to investigators and institutions about making consent forms more readable."

The bad news was that the forms were getting longer, she says.

"No matter how simple the wording on any particular paragraph, if you have a 22-page consent form, it's hard to believe the information might sink in with anybody," Kass says. "If you look at studies just geared to adults, the median length is 27 pages, which is a remarkable length."

This is one of the challenges IRBs face when trying to improve the informed consent process.

"What's frustrating with informed consent is that almost everybody recognizes that shorter and simpler are better, but there remain some very strong influences that I personally think have to do with liability," Kass explains. "This keeps consent forms much longer than anybody who is focused on proper understanding thinks is appropriate."

Participant understanding is another issue, and it wasn't addressed in that study.

"We simply looked at length of the consent form," Kass says.

"In another pilot study, a colleague and I did a follow-up to this," she says. "We're starting to look at interventions and doing some work where we give patients who are considering enrollment in a clinical trial a one-page fact sheet."

The fact sheet is user-friendly and has more readable language. For instance, it might say: "You are being asked to be in a research study. This study is looking at a new treatment for HIV in comparison to an old treatment. If you decide to be in the study you will be in it for a year," Kass says.

The one-page fact sheet was designed to be used by the research staff during study recruitment. The research nurse would go through the one-page sheet before discussing the entire informed consent document with study subjects.

"The idea was to have research nurses go through the consent discussion with the entire picture of the study before they're mired in details," Kass says. "The one-pager highlights any really important risks, but does not list 50-100 risks that might be outlined in the 27-page consent form."

The one-page form was designed based on the principles of learning with low literacy populations, she notes.

"There's only so much information people can take in at one time," Kass says. "It's not to say that other information is useless, but the best becomes the enemy of the good; people understand less."

The fact sheet is one intervention being tested. Another intervention involves requiring research nurses or enrollers to ask open-ended questions about the study at the end of the consent process, she adds.

"If the research participant doesn't say anything correctly, or if it's incomplete, it's an opportunity to go back and talk about more areas," Kass says. "We've done these interventions in a pilot study that showed promising results, and now we're trying to test these in a larger way." ■

Normalization of deviance can lead to problems

Education is key to ensuring ethics compliance

In order to protect human subjects and the integrity of research, everyone involved should adhere to ethics guidelines and must adhere to ethics and compliance standards. IRB members, investigators, lab workers, and others involved in trials have a large number of compliance rules to follow. But compliance can be a burdensome thing, and researchers who are under significant pressure can feel the strain and might let rule-following slide.

John Banja, PhD, a professor and medical ethicist at Emory University in Atlanta, refers to the "normalization of deviance" — a behavior he says is found in virtually every profession that requires adherence to rules and procedures. Employees will occasionally take shortcuts or not completely adhere to a policy or procedure. "It's not because they're bad people. But often they don't know what the rule is, or they feel enormous pressure to take shortcuts or do workarounds. They might feel that strict compliance with every policy, procedure, rule and regulation compromises their productivity, which they don't want to sacrifice at any cost."

"What we know from the published literature is that violations can range from mild to outrageous," says Banja. Violations might consist of reports not filed on time or informed consent not being signed or recorded appropriately, or they might involve falsifying reports or failing to report serious adverse events. "Oftentimes, too, investigators don't know what the appropriate regulation is and they'll think they're doing nothing wrong. Sometimes, you'll have research protocol going on for a few years, and people will leave and new investigators come on board who aren't entirely familiar with the protocol, and do things their way without checking the original protocol."

"We always will get a certain amount of reported events from unanticipated problems related to new drugs and devices, or new treatments where something different happens than before," says **Carlton Dampier**, MD, professor of pediatrics at Emory University School of Medicine. "We get a modest number of reports where the protocol wasn't completely followed, and we work with investigators to make sure they can develop a plan to do it better. If the protocol isn't feasible in the current structure, then we work with them to make sure they can be appropriately compliant."

Dampier and Banja sit on the Q, or Quality, committee of the IRB at Emory, which hears protocol deviations when they come to light. Investigators are expected to have a corrective action plan (CAP) in place to handle the issue, and usually that's all that's needed, Banja says. For instance, if an investigator discovers some sensitive files that have been misplaced in a non-secured storage area — which would be a HIPAA violation — the violation would be properly reported and the files would be

removed to a secure, HIPAA-compliant area. "On the other hand, if it's a very serious deviation, like falsifying documents or failing to report a serious conflict of interest, the transgression would have to be reported to various offices like our office of research integrity or the conflict of interest committee and probably reported to the sponsor," Banja says. "The ones that cause leadership at elite research institutions to lose sleep are when rule or regulation deviations endanger the welfare of research participants, corrupt research data, or flagrantly violate conflict of interest rules."

Institutions are continuously challenged to ensure that their conflict of interest cases are carefully managed. It is almost inevitable, Banja says, that the more successful you are as a researcher, the more likely you will have financial ties to the drug or device industries. "The more prestigious you are, the more likely you are to have a conflict. It's not necessarily wrong, but you have to take appropriate management steps. Conflict of interest committees and IRBs increasingly are getting more and more cautious and demanding with their researchers, and sometimes even forbid their getting involved with certain aspects of the research — like recruiting participants or interpreting data."

Compliance through education

With a multimillion dollar grant from the NIH's National Center for Advancing Translational Science, Emory University, Georgia Institute of Technology, and Morehouse School of Medicine have formed the Atlanta Clinical and Translational Science Institute (ACTSI). ACTSI launched six years ago, and the ethics program developed a website (http://www.actsi.org/ethics) containing dozens of ethical dilemmas in research including informed consent and privacy issues, data interpretation, drug trials, intellectual property, mentoring, and other issues. Dilemma submissions primarily come from graduate and post-doctoral students. Each dilemma is then followed by an expert opinion, in which the experts recommend a course of action. "[The site] gets hundreds of hits every month," Banja says. "It's a wonderful storehouse of ethical expertise. That's why we put it there — for professors and students to have some teaching materials featuring expert opinion."

Emory University's Office of Research Compliance conducts lectures and educational activities throughout the year, while graduate students at Emory University's Laney Graduate School are required to take an ethics course that consists of coursework and additional training from the students' departments. Post-doctoral students take a course on ethical issues as well that features discussions and case studies.

"This is part and parcel of creating a culture of research ethics and compliance. I think that we are doing a fabulous job in terms of teaching grads and post-docs on ethics and compliance. But I don't know if we are doing all that good a job with engaging our senior researchers with issues about compliance and ethics," Banja says. "There are some people who have been in the field 20 or 30 years and who may have developed bad habits, or feel the rules don't apply to them and think they haven't gotten to where they are by following rules."

Ensuring compliance probably works best as a top-down approach, Banja says, starting with leadership: administrators, supervisors, lab directors, principal investigators. "They are the people who really need to be impressed with ethics and compliance because they are the role models," he says. "The people who are in the trenches look to them for guidance and leadership."

A case can also be made, he says, for positive deviance — in other words, if there is a more efficient way of doing things, or if a rule actually gets in the way of patient safety. "We need to do a better job of changing rules and regulations that are truly inefficient and largely worthless to make life for researchers easier," Banja says. "I will tell you that rule following is one of the most burdensome kinds of chores they [researchers] have to do. Just staying abreast of new rules and regulations can be daunting, not to mention complying with them to the letter."

"You have this very interesting tension between innovation and vigilance and carefulness," he says. "Innovators are oftentimes risk-takers and sometimes push their creativity to limits. So, if a rule gets in the way they might look for way around it or simply ignore it. On the other hand, you have to protect patients and the quality of data. So, the tension between innovation and exquisite carefulness likely won't disappear any time soon." ■

Draft guidance outlines IRB responsibilities

Guidance defines role in vetting investigators

To better clarify the IRB's position in investigating clinical investigators and sites for clinical trials, the Food and Drug Administration (FDA) has released draft guidance for reviewing those qualifications.

While the points made in the guidance are nothing new, the FDA has made clear the role of IRBs in reviewing qualifications for IRBs that may be confused or unclear about the responsibilities.

"FDA has received questions from time to time about an IRB's responsibility for reviewing the qualifications of investigators and study sites," the FDA's Center for Drug Evaluation and Research (CDER) wrote in a statement to *IRB Advisor*. "FDA became aware, however, that some IRBs may be confused about their responsibility to review the qualifications of investigators and sites after recent findings that some IRBs approved studies without checking the qualifications of investigators and/or adequacy of sites identified in the study materials. FDA thought it was important to issue a reminder to all IRBs about these responsibilities."

Though the information isn't new, some IRBs welcome more clear guidelines from the FDA."I think that a lot of the regulations refer to the sponsor's requirements and some IRBs may think the onus is on the pharmaceutical sponsor," says **Raffaela Hart**, BS, CIP, CIM, senior director of IRB and IBC services at the Biomedical Research Alliance of New York (BRANY). "This does say in a clear way that the IRB has a part of the responsibility. It's a great way to understand the FDA's interpretation of the regulations, and shows more consistency across the IRBs. We hear all the time about how there's no good way to know if IRBs have a consistent way of doing things, and these guidelines really help in that regard. If we know what their [the FDA's] expectations are, we can consistently apply them."

"What's new to me is that the FDA is formalizing what's been expected all along," she continues.

While the FDA places much responsibility on the trial sponsor to select qualified investigators, the draft guidance describes the IRB's role in the selection.

If the IRB has no previous relationship with the investigator, the IRB should obtain statements of qualification from other institutions. Additional steps, such as reviewing medical licensure, may also need to be taken.

"Another consideration is that a sponsor may not be aware that an investigator is conducting other studies in addition to the sponsor's," according to CDER. "The IRB, on the other hand, would be more aware of the other studies a particular investigator is conducting, the size of the investigator's staff, other commitments the investigator may have that could impact his/her ability to conduct the study, etc."

The document uses this example: "If the reviewing IRB has no knowledge of either the clinical investigator or the institution (e.g., the IRB is not affiliated with the institution where the research will be conducted; the IRB has no previous experience with the investigator), the IRB would likely need to take additional steps to evaluate the investigator's qualifications (e.g., reviewing the curriculum vitae of the investigator, subinvestigators, and other necessary study staff; verifying professional associations and medical licensure; reviewing relevant publications)."

Pay particular attention to an investigator's experience and training related to the specific study, particularly if the study is high risk.

"The regulations state that in order to approve FDA-regulated research, each IRB must determine that all of the criteria for approval have been met, including that 'risks to subjects are minimized' and that 'risks are reasonable in relation to anticipated benefits, if any, to subjects...' (See 21 CFR 56.111(a)(1) and (2).) An integral part of these determinations includes evaluation of the investigator's qualifications and the adequacy of the research site. If an IRB fails to evaluate either of these, subjects could be placed at unreasonable and unnecessary risk," according to CDER.

The IRB's responsibilities for determining the eligibility of a study site is also described.

For example, "If a proposed clinical investigation involves administration of medical procedures by qualified healthcare providers using medical equipment, the IRB should be prepared to assess the adequacy of the facility's staff and equipment, including the availability of emergency or specialized care if the need should arise. If the proposed research site is part of a major medical institution, the IRB would likely be able to simply note that fact. If, however, the IRB is unfamiliar with the proposed investigational site, the IRB would likely need to confirm whether the site is appropriately staffed and equipped to conduct the proposed research. The IRB should be able to

obtain a statement from an appropriate person or persons at the research site or institution stating that the facilities are adequate."

BRANY requires that potential investigators submit curriculum vitae and provide training-related documents. The IRB also checks with the FDA to make sure the investigator has never been disqualified from research. "There are a number of ways to look for red flags in terms of documentation," Hart says. "We look at the CV to ensure they have adequate training for what they want to do and have experience in that area. There have been instances where our IRB has questioned whether someone was qualified, and we had to request a change of investigator."

"We ask for a lot of information — we're an independent IRB and many facilities may use us," Hart continues. "There are questions on the applications about the facilities, their procedures for emergency responses."

When it comes to delving deeper into an investigator's qualifications, "definitely don't be afraid to ask questions," Hart says. "Some investigators may have experience but may not adequately document in their CV. Don't be afraid to ask for information on their qualifications. We found a lot of useful information in databases on licensure information, such as whether a license has ever been suspended or put on probation."

The FDA's Guidance for IRBs, Clinical Investigators, and Sponsors can be found at http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM328855.pdf. ■

Study: Bias in reporting of breast cancer trials

But no industry influence indicated

A study by Canadian researchers shows that many published breast cancer studies are biased to show a positive outcome.

The study, published in *Annals of Oncology*, looked at the quality of reporting the primary endpoint (PE) and toxicity of randomized clinical trials of breast cancer drugs. The authors searched PubMed for publications between January 1995 and August 2011, excluding trials with sample sizes less than 200, commentaries, review articles, ongoing studies, and articles for which only the abstract was available. For the study, "bias" was defined as "inappropriate reporting of the PE and toxicity, with emphasis on reporting of these outcomes in the abstract," and "spin" defined as "use of reporting strategies to highlight that the experimental treatment is beneficial, despite a statistically non-significant difference in the primary outcome, or to distract the reader from statistically non-significant results."[1]

The researchers from the Princess Margaret Cancer Centre looked at 164 published trials. Of those, 33% showed bias in primary endpoint reporting and 67% in the reporting of toxicity. The primary endpoint was more likely to be reported in the concluding statement of the abstract when significant differences favoring the experimental arm were shown; 59% of 92 trials used a secondary endpoint to show drug benefit when the primary endpoint was not achieved. Only 32% of articles indicated the frequency of grade 3 and 4 toxicities in the abstract. A positive primary endpoint was associated with underreporting of toxicity.[1]

"[S]pin was used frequently to influence, positively, the interpretation of negative trials by emphasizing the apparent benefit of a secondary end point," the researchers note.

Most studies were published in prestigious medical journals, the study authors found. Thirty trials were included in ClinicalTrials.gov, and among those, the primary endpoint was changed in the final report in seven studies. Industry funding was reported in 103 studies, 32 studies were funded by academic or governmental grants, and funding source was not stated in 29. While the majority of the examined studies were funded by industry partners, the authors state "we found no association between industry sponsorship and biased reporting of either efficacy or toxicity, and no association of for-profit sponsorship with change of the PE between that listed in trial registries and the final publication."[1]

"[B]ias in the reporting of efficacy and toxicity remains prevalent. Clinicians, reviewers, journal editors and regulators should apply a critical eye to trial reports and be wary of the possibility of biased reporting. Guidelines are necessary to improve the reporting of both efficacy and toxicity," the study authors concluded.

REFERENCE

1. F. E. Vera-Badillo, R. Shapiro, A. Ocana, E. Amir, and I. F. Tannock. Bias in reporting of end points of efficacy and toxicity in randomized, clinical trials for women with breast cancer. *Ann. Onc.* January 2013: mds636v1-mds636. ■

Patient recruitment and retention rates struggle

A new study has found that while nine out of 10 clinical trials worldwide meet enrollment goals, reaching those goals could mean doubling original timelines.

The research from the Tufts Center for the Study of Drug Development (CSDD) looked at 150 clinical trials from more than 16,000 trial sites worldwide.

"Patient recruitment and retention are among the greatest challenges that the clinical research enterprise faces today, and they are a major cause of drug development delays," says **Ken Getz**, director of sponsored research at Tufts CSDD. "The results of our recent study paint a complex picture of global practices and their effectiveness and characterize a very high level of investigative site performance risk." (More information on the study can be found at http://csdd.tufts.edu/.)

The study also found that most drug sponsors and contract research sites rely on a limited number of traditional recruitment strategies, such as physician referrals and media such as television, print, and radio ads, and have not yet embraced social media and other new or non-traditional methods.

Other study findings include:

• 89% of all clinical trials meet enrollment goals, with site activation rates reflecting success with study startup and speed to recruit the first patients.

• The highest site activation rates are in Western Europe (93%), Eastern Europe (92%), and Asia/Pacific (91%).

• Enrollment achievement rates vary by region, ranging from 75% to 98% of targeted levels, with Asia/Pacific and Latin America achieving the highest rates.

• Eleven percent of sites in a given trial typically fail to enroll a single patient, 37% under-enroll, 39% meet their enrollment targets, and 13% exceed their targets. ■

Income tied to cancer study participation

Low-income cancer patients, including those who are on Medicare, are far less likely to participate in clinical trials than higher-income patients, according to a study in the *Journal of Clinical Oncology*.

Researchers from the Fred Hutchinson Cancer Research Center in Seattle looked at the socioeconomic and demographic information of 5,499 patients who participated in trials from 2007-2011. Patients were surveyed via an Internet-based treatment decision tool, using items about treatment, tolerability of treatment, convenience, and cost.

Of those patients, 40% discussed clinical trials with their physician, 45% of those discussions led to offers of clinical trial participation, and about half of those offers led to trial participation. Overall participation, however, was 9%.

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

■ E-security grows as major issue

■ Improve IRB efficiency

■ Lessons learned in disaster preparedness

■ Spotlight on children's hospital IRB partnership

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Univariate models showed that patients with lower income and education were less likely to participate, including older patients on Medicare. In multivariable models, income was a significant predictor of participation. Low-income patients showed far more cost concerns.[1]

"A better understanding of why income is a barrier may help identify ways to make clinical trials better available to all patients and would increase the generalizability of clinical trial results across all income levels," the study authors note.

REFERENCE

1. Unger JM, Hershman DL, et al. Patient income level and cancer clinical trial participation. *J Clin Oncol*. 2013 Jan 7. [Epub ahead of print] ■

CNE/CME QUESTIONS

1. Most IRBs measure the time it takes to complete an IRB review. Which of the following would be another good item to measure?
   A. Total submissions
   B. Number of exemptions
   C. How many submissions are screened and then returned as not requiring further review
   D. All of the above

2. Which of the following is not among the guiding principles for creating an efficient, user-friendly protocol submission form?
   A. Write clearly and plainly.
   B. Create forms that can be audited.
   C. Target questions to the expected user.
   D. Make sure key questions are duplicated between submission form and other forms.

3. Over the past two decades, informed consent forms have been shortened, but their readability has worsened.
   A. True
   B. False

4. According to John Banja, PhD, professor and medical ethicist at Emory University, normalization of deviance occurs when:
   A. An employee may not know what a particular rule or regulation is.
   B. Employees feel greatly pressured to take shortcuts.
   C. An employee does not want to sacrifice productivity.
   D. All of the above.