Follow OHRP reporting guidelines
Agency spells out how and when to report adverse events

In late May, the OHRP updated its guidance document on when and how it must be notified of adverse events. The biggest change, says Adil Shamoo, PhD, bioethicist at the University of Maryland School of Medicine, is that OHRP will now respond in writing to adverse event reports.

That written response will tell the institution whether the agency feels that the facility's corrective plan addresses the cause of the adverse event and will prevent future occurrences. OHRP also says in the document that corrective actions that an institution says it will take in an adverse event report will sometimes need to be made institutionwide.

The fact that OHRP will respond in writing caught Shamoo's attention when he first saw the guidance document, he says. It shows that OHRP will look closely at the remedies research institutions take for fixing what has already happened and for preventing future adverse events.

The fact that OHRP will reply formally, in writing, and comment on the adequacy of the remedies underscores how intently the...
OHRP guidelines

OHRP will scrutinize research institutions moving forward, Shamoo adds.

"It codifies the responsibility of the research organization of adverse event reporting and potential consequences," he says.

Other than stating that the OHRP will respond to reports in writing, the remainder of the document restates existing regulations for the most part. Because most of the document is a restatement, it's not big news, Shamoo explains, but in another way, it's important because of the one major change.

The document not only covers adverse event reporting, but also any

- unanticipated problems involving risks to subjects or others
- serious or continuing noncompliance with IRB requirements or determinations
- suspension or termination of a study's IRB approval

Further guidance

Aside from the writing component, Shamoo calls the document a "minor clarification" of OHRP policy on adverse event reporting. The document combines information that might have been hard to find—or separated in several different places—among the OHRP regulations. But Shamoo says he still sees the need for a national reporting system (see story on p. 5).

Aside from the above revelations about institutional responsibilities in addressing adverse events, other items in the document give more insight on OHRP's expectations for adverse event reporting.

First, a flow chart helps investigators, institutions, and IRBs figure out which events the agency expects them to report. The chart helps untangle complexities in NIH v. non-NIH-funded studies, and the involvement of federalwide assurances, in which an entire institution pledges to stick to regulations governing its research.

Second, the guidance outlines the exact information it expects in the different reports (i.e., reporting adverse events in a study v. termination of a study's IRB approval).

OHRP will then respond

Finally, the document offers a little clarification on the timing of reports, but still leaves some room for differing interpretations.

"The regulations at 45 CFR 46.105(a) and (b)(5) do not specify a time frame for reporting, except 'promptly,'" according to the OHRP. "For a more serious incident, this may mean reporting to OHRP within days."

"For a less serious incident, a few weeks may be sufficient. It may be appropriate to send an initial report and indicate that a follow-up or final report will follow by the earlier of [1] a specific date; or [2] when an investigation has been completed or a corrective action plan has been implemented," according to the guidelines.

Organizations filing reports can expect the following process going forward. Once an institution files its report to OHRP, Shamoo says, OHRP will then respond in writing—the new part of the process that this document unveils.

Investigators at small sites where a single investigator might also be "the institution" should pay particular attention to these reporting requirements, he says, as this document applies directly to them.

"They'll issue a written response to say whether the report outlines corrective action that was adequate or not," Shamoo says. "It's just like the warning letters. Basically, they're going to respond to those incident reports in writing."

See the new OHRP adverse event reporting guidelines in their entirety at www.hhs.gov/ohrp/policy/incidreport_ohrp.html.

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Ethics expert calls for reform of adverse event reporting system

Patients involved in research often experience adverse events ranging from trivial side effects to serious adverse events up to and including, in rare cases, death. It's a risk they take to test an experimental treatment.

People considering joining a clinical trial should know about the likelihood of adverse events that happen overall in clinical research.

Yet such adverse events are grossly underreported, says Adil Shamoo, PhD, bioethicist for the University of Maryland School of Medicine, and this underreporting minimizes the appearance of such risks.

On June 13, the ORHP issued new guidance on adverse event reporting, but Shamoo says it doesn't go far enough. He calls for further changes to a reporting system that he says is to blame for "serious gaps in the ethics of conducting clinical trials" because it fails to communicate the real risks of research to subjects in clinical trials.

"The whole field of adverse event reporting needs standardized reporting, a national data bank, tracking of trends and safety profiles, and there should be a single, federal oversight and management agency," Shamoo told CTC in an interview in July.

In an article published in the April issue of the Drug Information Association's DIA Today, Shamoo cites ORHP, CenterWatch, Institute of Medicine, and FDA statistics that he first compiled for a 2001 Accountability In Research article that point to the underreporting of adverse events on a large scale.

According ORHP, researchers reported eight deaths and 386 adverse events among the 70 million people who participated in federally funded trials in 1990–2000. Assuming that the average person participated in a trial for one month, and comparing it to statistics for general clinical care, Shamoo says 5,000 people would have been expected to die and that more than 50,000 adverse events should have occurred.

"Based on, among other things, the above statistical averages, scholars believe that the reporting of adverse events has not been accurate," Shamoo says.

No national clearinghouse

The problem stems from the fact that different agencies have different reporting requirements, and some of them are vague, he says.

If a national informational clearinghouse could collect, sort, and make adverse event information consistent and accessible to the research community, healthcare industry, and public, it would make research safer and more credible.

"In the near future, there ought to be a serious effort to modify adverse events reporting such that is simplified, uniform, clearly defined, single time frame, and more importantly containing the same or very similar parameters," Shamoo says. "The communication of information regarding clinical trials, including adverse events, would enhance participation in clinical trials and increased public confidence in the system."

News in Brief

Partnership aims to improve minority clinical trials participation

Baylor College of Medicine is teaming with biotech firm Genentech and the Intercultural Cancer Institute to improve the participation of minorities and underserved patients in clinical trials, the college reports.

Genentech is providing $5.5 million over four years to support the program, which aims to improve public policy and clinical research involving minorities, since they are typically underrepresented in trials, according to the report.

The program comes on the heels of the FDA approval of the heart failure drug BiDil, the first drug with an indication specifically for African-American patients.
Traps  < p. 1

ties, while others can lead directly to jail time and civil penalties.

"We asked about 33 different kids of behaviors," says Martinson. He and his colleagues developed a list
from polling scientists in focus groups.

"We were convinced that focusing on fraud behavior really missed a lot of things that were going on out
there, sort of lower-level but questionable research practices that could certainly be damaging to the integrity
of science," he said. "Although they don't necessarily cause us to call into question the entire scientific
record, they really are corrosive in a number of ways."

System partly to blame

In any profession, there are likely a few cheats and frauds trying to get away with something. But
when more than 15% of respondents op to changing their research methods for the benefit of the study
sponsor, admit to insufficient recordkeeping, or even dropping data points and observations from an analysis
based on the "gut feeling" that their were wrong, Martinson says it is no longer an isolated problem.

Martinson theorizes that part of the blame for such practices lies with the way the field incentivizes and
commercializes career advancement—and fosters competition for ever-dwindling resources. His survey broke
out stats according to early-career scientists vs. those in mid-career, and overall.

Interestingly, mid-career scientists admitted to engaging in more misbehaviors than those in their
disline careers—with a few exceptions. For this survey, mid-career typically meant that a researcher was in his
or her mid-40s with one or two NIH grants as principal researchers.

"People have learned they need to do [these unethical things] to stay competitive or . . . people felt pressured to do to get an edge, to get ahead, or to stay ahead," Martinson says.

His study is the first to quantify how widespread questionable ethical behaviors are in the scientific
community. He hopes that showing how common these transgressions are will be enough to prompt
thinkers in this field to begin brainstorming ideas about how to correct the system because it causes "good people to behave in ways that they themselves
don't want to behave in."

"You want the best behavior out of scientists, but it's clear they're being pushed to do things that are sub-optimal, which I think is an appropriate word [to
describe the lesser ethical breaches covered in his study]," Martinson says.

Fixing the system

Martinson's opinion is that research represents a failed market because it fosters an environment in
which researchers feel they need to engage in unethical behaviors to maintain their employment.

Where do you draw the line?

The following list is a breakdown of the results of the anonymous survey conducted by Brian
Martinson, PhD. The list includes the percentage of researchers who admitted to each of the "ethically
questionable behaviors about which they were polled:

- 27.5%: Inadequate recordkeeping on research projects
- 15.5%: Changing design, methodology, or results of a study under pressure from funding source
- 13.5%: Using inadequate or inappropriate study designs
- 12.5%: Overlooking others' use of flawed data or questionable interpretation of good data
- 10.8%: Withholding details of methodology or results in papers or proposals
- 1.4%: Engaging in relationships with students, subjects or clients that may be seen as question-
able
- 0.3%: Cooking (falsifying) research results

Note: Although Martinson was careful to fully anonymize results from this NIH-funded survey, the
author suspects that these figures—especially for the more egregious behaviors—are low because some
respondents might have feared that somehow regulators could hunt down investigators admitting to
wrongdoing.

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Page 4 © 2005 HCPro, Inc.  Clinical Trials Compliance—August 2005
How do you fix this problem? Martinson agrees with executive director of the American Society for Cell Biology, Elizabeth Marincola, PhD.

She advocates that more experienced scientists should give junior researchers in training a better idea of their job prospects—that not every one will be able to derive full-time employment from research funded by the government and private sector.

Marincola says researchers need to be trained more broadly to take jobs in industry, business, government, and the media so they have more choices when they hit that ethical crossroads where one path leads to falsifying data (or cutting a lesser corner) and career advancement, and the other to the unemployment line.

Martinson adds that broader training for scientists will also help the “brain drain” of good scientists in the latter group leaving the field.

To Martinson, these scientists represent a waste of well-trained, intelligent people who the field is losing forever because of a broken system.

“We have to stop thinking that the only viable career for a scientist is running an NIH-funded research shop,” Martinson says. “There just are not enough positions to do that.”

Editor’s note: Read Martinson’s Nature study in its entirety at www.nature.com/nature/journal/v435/7043/full/435737a.html.

### News in Brief

**Judge: Amgen does not have to give halted trial drug**

A federal judge last week denied a request from two patients to order biotech company Amgen to continue supplying an experimental drug from a discontinued clinical trial, The New York Times reports. Though the trial was halted, the patients said the drug relieved their Parkinson’s symptoms, says the report. The judge ruled that Amgen was under no contractual obligation to continue supplying the drug and that the informed consent forms which the patients signed specifically acknowledged Amgen’s right to terminate the trial, says the Times.

### Federal policy on misconduct

The U.S. Office of Science and Technology offers detailed policies regarding research misconduct. It defines misconduct as:

- **Fabrication:** Making up data or results and recording or reporting them
- **Falsification:** Manipulating research materials, equipment, or processes or changing or omitting data or results such that the research is not accurately represented in the research record
- **Plagiarism:** The appropriation of another person’s ideas, processes, results, or words without giving appropriate credit

It does not include honest error or differences of opinion.

Once someone levies allegations of misconduct against a researcher, authorities will investigate them to determine whether

- there was a significant departure from accepted practices of the relevant research community
- the researcher intentionally, knowingly, or recklessly committed misconduct
- the allegation can be proven by a preponderance of evidence

Depending on the seriousness of the misconduct, NIH-funded investigators might have to do as little as correcting the research record or as much as serving jail time and paying civil penalties.

View the full policy—which also details the process for reporting misconduct—at www.ostp.gov/html/001207_3.html.
Recruit and retain the best research coordinators

It pays to give coordinators a reason to stay

Finding research coordinators whose working style dovetails with your own can be difficult and training them time-consuming. But once they are on staff, the real challenge is keeping them there.

Your organization will benefit greatly if you are successful at keeping experienced coordinators on staff. Experienced coordinators work more efficiently, are more productive, make fewer mistakes, and take more initiative in solving problems. As such, their presence—and absence—affects your bottom line, said Wanda Kay North, MBA, RN, CCRC, CIM, during a presentation at the Association of Clinical Research Professionals 2005 North American Conference and Exposition in Orlando, FL, in early April. She is manager of research programs at St. Joseph’s/Candler Health System in Savannah, GA, and is an ACRP trustee.

“Keeping good, quality coordinators may be one of the most troublesome problem facing managers in research,” North said. “If you’ve not had this problem, chances are you will in the future.”

By “keeping,” she means keeping staff happy and, by extension, keeping them employed with you. In the current market, a good research coordinator often has many job choices—including other research coordinator positions and jumping over to the drug companies and becoming a site monitor. Staff don’t have to stay at your facility if they aren’t happy.

Make it your goal to keep your staff happy. One way to do that is to develop a “clinical ladder” program, which provides coordinators with goals and incentives for improvement. This can help keep coordinators invested in staying at your site. In addition, be patient during the pre-hire interviewing process to weed out coordinators who seem likely to quit, North says.

Why they’re difficult to lose

Getting a research coordinator up to speed at your facility takes time and money, North says. But once these coordinators are in place, replacing them costs even more—in lost hours to the investigator helping fill in gaps in staffing and searching for and training the coordinator’s replacement.

“It distracts in the research environment when someone else has to pick up the workload,” North said. “Turnover sucks up resources and money better than a vacuum cleaner.”

Retaining coordinators, however, doesn’t have to deplete money and resources. North suggests, in fact, that money isn’t the primary motivator that keeps coordinators at your site. Instead, it’s recognition—which includes the opportunity to advance.

Recruiting

North offered the following strategies for recruiting good coordinators:

* Hire talent, not necessarily experience. Hire
talented people who can grow and fit into a coordinator position. Look for a candidate with organizational skills who can prioritize, critical thinkers, good time managers who possesses patient assessment skills, a good manager, and independent workers who have the ability to work without a lot of hand-holding from supervisors.

- **Hire people with certain personality traits.** If a person has a can-do attitude, he or she is more likely to be satisfied and keep plugging away during hard times in the thick of deadlines. As North puts it, “We can hire the attitude and train the skills, but you can’t hire the skills and train the attitude.”

- **Bolster your reputation.** If your facility is known as a top-notch research center, you’ll attract top-notch people. Your organization’s values must be known and practiced by all staff, every day. The reputation of your facility as a good work environment will spread outside the office—and make it desirable to the best research coordinators.

The most important trait in research coordinators—and perhaps the key to retention—is solid leadership skills. These candidates are better equipped for the job.

“Aim high, and don’t allow yourself to settle for any warm body,” North says. “It’s very easy to want to fill your coordinator position as quickly as possible . . . but if they are not the right candidate, you spend valuable time, resources, and money for a person who ultimately will leave in six months to a year.”

**Retention strategies**

So how does an investigator keep a coordinator around once he or she has found that golden candidate to fill the position? First ask yourself the following questions about your current coordinator staff, and address any to which you answer no, North says. Taking action so that you can answer all with a yes is the first step to retaining the coordinators you have—and the good ones you’ll hire in the future after following the above interview techniques.

Do your coordinators

- know what is expected of them?
- have the resources they need?
- have the opportunity to do what they do best, every day?
- receive recognition or praise in the last seven days?
- know that their opinions matter in the workplace?

Once you’ve answered those questions, consider bolstering other aspects of your research site:

- **Make the orientation complete.** Chances are, if turnover’s going to occur, it will happen within six months. Get your new coordinators off to a running start with an upbeat, detailed orientation.

- **Offer a clinical ladder.** Make new candidates feel like the valuable part of the organization that they are by providing a clinical ladder for them to climb, preferably one that the coordinators themselves helped design. The plan should offer a series of achievement “rungs,” each of which include special recognition for coordinators whose work with research participants is exceptional and goes beyond the scope of their job descriptions. Rungs can include community involvement, publication of articles, or specialty certifications within research.

- **Support professional development.** Once you’ve established a clinical ladder, inspire coordinators to climb it. Encourage coordinators to set realistic career goals, and offer help in achieving those goals by offering support, paying for their extra education and professional association memberships, and giving cash incentives when they reach a particular goal.

- **Treat them as your most valuable asset.** Whether your facility offers a clinical ladder or not, don’t forget that research coordinators actually conduct the study work and make your studies “go.” Give them the credit they deserve; recognition pays off in improved performance and increased job satisfaction.

“Recognition and awards are more powerful than money,” North said. “Money’s important, but you need to find ways to recognize your coordinators’ contribution to the organization, and don’t settle for any temporary incentive plan. You need to have a recognition program that has meaning to the coordinators . . . ask them how they want to be recognized. When people are encouraged, they take pride in their responsibilities.”
Get some guts: Strong leadership can turn your practice into a winner

If your organization is efficient but seems to have a black cloud over it, stop hiring people based on skill and start hiring them for personality, said Kevin Freiberg, EdD, a motivational speaker who presented during the Radiology Business Manager's Association 2005 Radiology Summit in Las Vegas in June.

Freiberg, coauthor of the book Guts! Companies the Blow the Doors off Business-as-Usual, says one bad employee can sour an entire workplace, drag down the organization's culture, and harm your bottom line.

Turn your culture around by hiring positive people who will bring an entrepreneurial spirit to your facility and go out of their way for your customers.

"Bad attitudes suck the life out of practices," Freiberg said.

Many organizations make the mistake of focusing on skill instead of personality. When you hire a new employee, look for someone who will be positive and motivate others.

"Hire for attitude, train for skill," Freiberg said, adding that you can bring someone up to speed on the technical aspects of the job, but you cannot give someone a new personality.

In the end, an individual's personality will define his or her job performance. "You will hire people for what they do, but you will fire them for who they are," Freiberg said.

And getting rid of a bad employee is a potentially expensive and difficult task. "We all do more with less. Can you really afford to make a bad hiring decision?" Freiberg asked.

To avoid hiring mistakes, focus on your job candidates' character. Freiberg separates employees into four main categories—those who add, subtract, divide, and multiply.

The adders and multipliers are your go-to employees—those you can count on to get the job done. The substractors and dividers are the ones you need to weed out. Keeping them on staff will bring everyone else down.

Although it may seem impossible to hire for attitude and only choose adders and multipliers based on short interviews with people on their best behavior, Freiberg says it is entirely possible. The key is to ask the right questions to get an inkling about attitudes (See a list of suggested interview questions on p. 9).

There are several attributes to look for when interviewing potential employees, but the most important one to look for is the "fun" factor. You want people on staff whom are pleasurable to work with, Freiberg said. We all like to have fun at work, and hiring fun people will help boost your facility's spirit.

Establishing an enjoyable workplace environment may have the added benefit of bringing in better employees because a positive place to work will increase the number of people who want to work at your facility.

Making solid hiring decisions can be difficult if you don't get a decent pool of applicants. But if you define your organization as a great place to work, candidates will come to you.

The Southwest story

Consider Southwest Airlines, an organization that Freiberg said has an outstanding corporate culture and has established itself as a great place to work.

In 2004, the company interviewed 33,000 people for 5,134 new jobs. "It's easier to get into Harvard than it is to get into Southwest Airlines," said Freiberg.

How can you create an equally attractive work environment? "Help your people feel heroic about what they do," says Freiberg. "Those types of work environments are so rare, which makes them so appealing."

Remember to focus on your own attitude and how it affects your business. Ask yourself the following questions:

- What are you learning today that will add value tomorrow?
- What have you learned in the past three weeks that would add value to the people who you serve?
- When is the last time you studied the winners in areas where you need to improve?
- What was the last best practice you adopted?
If you can’t answer these questions, ask yourself another one: “Why shouldn’t your employer outsource your position?”

Remember that happy employees will help your organization perform better.

“At the end of the day, the thing that separates your practice from others is your people,” Freiberg said.

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**Hire for attitude, train for skill**

The following questions were developed by [Drs. Kevin and Jackie Freiberg](https://www.freibergs.com) to help interviewers find positive employees who will add to an organization and weed out negative candidates who have the potential to sour the work environment. The words inside the brackets indicate what type of information the question seeks to elicit from the candidate.

- Tell me about the last time you broke the rules to serve a customer in need. [flexibility; judgment]
- Tell me how you recently used humor to diffuse a tense situation. [fun]
- Tell me about a time when you went above and beyond the call of duty to assist a coworker when you received no recognition or no credit. [unselfishness; teamwork]
- Give me an example of how you work with an extremely difficult coworker. How did you handle it? [adaptability]
- Describe a time when a coworker failed to pull his or her weight. What did you do? [adaptability]
- Tell me about a time when you made a serious mistake with a customer or coworker. How did you reconcile it? [ability to admit mistakes]
- Tell me how you handled the most difficult customer you’ve ever dealt with. [service focus]
- What’s the most important thing you have learned in the past six months? What new skills, knowledge, or experience have you gained? [willingness and ability to learn]
- Tell me about the last time you tried something new or took on additional responsibility when there was no guarantee for success. [willingness to take risks]
- Tell me about the last time you asked someone for feedback. What did you do with that information? [willingness to be coached]
- Tell me about the last time you had to work with others to accomplish a critical result. What did you do? [collaboration]

Another exercise you can use to screen for unselfishness and teamwork begins with asking interviewees to prepare five-minute presentations about themselves for a group interview.

As each presenter comes up to share his or her personal story, watch the audience members to determine whether they enthusiastically draw the speaker out and encourage him or her [unselfishness] or whether they make last-minute notes for and prepare their own presentations [selfishness].

Note that these questions are not hypothetical (i.e., what would you do?) questions. These questions ask for previously demonstrated behavior as a means to determine future success.

Your questions will become more powerful and targeted if you first identify your star players in a particular function and then build a profile of the key attributes that are common to each of them. Successful screening begins with knowing precisely for what it is you’re looking.

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*Editor’s note: The Freibergs are professional speakers and authors of the recently released GUTS! Companies That Blow the Doors Off Business-as-Usual and bestseller NUTS! Southwest Airlines’ Crazy Recipe for Business and Personal Success. To read more about Drs. Kevin and Jackie Freiberg, please visit their Web site at www.freibergs.com.*
Noncompliance news

FDA warning letters become more detailed as inspectors drill deep into study records

Editor’s note: This column examines enforcement actions taken in response to noncompliance and offers tips on helping your organization avoid the same pitfalls. This month’s analysis looks at an FDA warning letters sent May 26 and June 6 to research sites in Baltimore and South Euclid, OH.

A Baltimore clinical investigator, Niel Constantine, PhD, received a warning letter from the FDA May 26. Among the regulatory compliance problems inspectors found during their late January–early February inspection of his device trial were the following:

- The study didn’t document the age of some subjects, and some of the subjects were younger or older than the protocol’s specified 18–55 age range.
- Screening was required for certain subjects to ensure that they didn’t have life-threatening illnesses and immunosuppression before joining the study, but this screening wasn’t documented.
- The study protocol called for certain blood tests during a patient’s visit. Blood was collected at the visit, but the staff didn’t conduct the necessary tests until up to eight days later.
- Not all of the subjects who needed counseling as per the protocol received it.
- The study required that 1,000 test kits be stored at 15 to 30 degrees Celsius; no documentation showed that this requirement was met.
- The sites involved in the study failed to keep full case reports for each subject.
- Constantine did not file all of his required reports to his IRB.
- Constantine did not file a complete final report to the study sponsor.

This warning letter was the second issued to Constantine by the FDA in a six-month span. He received a first letter in November 2004, for a different study. That case was resolved when he submitted an “adequate” corrective action plan.

Cleveland drug study warned

Robert Hosroffer, DO, of South Euclid, a Cleveland suburb, received a warning letter June 6 regarding his drug study, which the FDA inspected in February and March.

Inspectors focused on the following compliance issues:

- Including subjects in the study who weren’t eligible
- Failure to report serious adverse events to the IRB, including one case where a subject spent a day in the hospital with vomiting and abdominal pain
- Failing to collect paper and electronic patient diaries required by the protocol
- Drug disposition and accountability issues

Furthermore, the protocol specified that the study drug should be injected in one to four sites on the patients’ bodies, depending on the amount of the drug they were to receive. Inspectors found that in many cases the drug was injected at more sites than indicated by the protocol.

Responding to inspectors

In reading both of these warning letters, Tamara O’Black, CIP, regulatory affairs administrator for Park Nicollet’s human subjects’ protection program, saw a couple of lessons for investigators who want to avoid stepping into the same regulatory traps.

First, an investigator’s reply to the inspectors’ 483 form outlining compliance issues is an opportunity to show the FDA that he or she plans to address problems in an orderly, complete manner.

“To me it seems that in both of these cases, there seems to be a loss of opportunity,” she says. “Really, what the FDA is looking for is a thorough, accurate response that’s going to include full disclo-
sure, acknowledgement of any questionable practices, and a really thoughtful, complete plan for correction."

Investigators who follow up with such answers to their 483s can possibly head off warning letters and, at the same time, strengthen their research programs, O'Black adds.

In Hostoffer's case, the warning letter implies that the investigator provided information that contradicted study documentation in his reply to the 483, O'Black says. This may have given regulators the impression that the investigator didn't take the inspectors' findings seriously or, perhaps, kept sloppy records.

In Constantine's case, he missed a huge opportunity demonstrate how seriously he took those issues in previous inspections, she says.

"When the FDA starts referring to things as a 'pattern' of behaviors, it should be a huge red flag," O'Black said.

If you are proactive, it will show returning inspectors that you are making progress toward improved compliance. Not everything has to go perfectly, she says—you just must show that you've self-diagnosed problems and take their resolutions seriously.

**Devil's in the details**

These warning letters also reflect a new level of detail that the FDA seems to have added in 2005, with long tables matching regulatory violations to specific subjects and dates, says O'Black.

That's partially because the FDA is trying to be more transparent in their dealings with investigators, O'Black says. The agency probably feels it needs to be more detailed in its findings because of pressure from public legislators and the media.

"They're mapping it out in detail to the level of things we might not see included on a 483 before," she says.

O'Black says investigators should note that these letters show that inspectors will ferret out questionable practices such as

- forms with blanks prefilled
- having someone besides the person who signed the form date it
- not signing things at all (in the case of Hostoffer, the reply to the 483 as well as the protocol-required subject consent forms) that needed to be signed either by regulation or protocol.

Lastly, the Constantine warning letter shows how critical it is to ensure proper documentation.

"Although it is correct that there was no documentation showing that records were reviewed by me, I would like to assure you that I was closely following the daily activities and have been in constant touch with the director of the clinical trials," the warning letter quoted Constantine as saying in his reply to the inspectors' 483.

How did the FDA reply to that?

"Without contemporaneous, written documentation, however, we have no way to review how consistently and thoroughly you monitored all study results and assured compliance with the study protocol, as the protocol required you to do," the warning letter states. "Please understand that for your promise to 'document your oversight activities' to be meaningful, that documentation must be contemporaneous and sufficiently detailed for investigators to review what you did."

It's doesn't matter how much you talk to a subject or how well they understand the protocol, unless there's documentation that proves you did, FDA inspectors won't be satisfied, O'Black says.

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**Questions? Comments? Ideas?**

Contact Managing Editor Kelly Bilodeau

Telephone: 781/639-1872, Ext. 3298  E-mail: kbilodeau@hcpro.com

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Mayo Foundation settles for $6.5 million amidst allegations that researchers mismanaged grant funds

In late May, the Rochester, MN–based Mayo Foundation—parent of the Mayo Clinic—settled a case with the U.S. Department of Justice (DOJ) by paying the government $6.5 million.

Among the allegations were improper transfer of grant funds. Although Mayo admitted no wrongdoing, the DOJ said that investigators found evidence of improperly transferred expenses as well as “an accounting system unable to monitor and manage charges made to federal grant awards in the manner required by federal law.”

“Today’s settlement demonstrates our commitment to vigorously pursue allegations of fraud and abuse in federal grant programs,” said Peter Keisler, assistant attorney general for the civil division of the DOJ, in a press release. “All recipients of federal grants must comply with the restrictions placed on the use of that grant money.”

Such allegations can incur more than just one-time costs to settle. According to an Associated Press story published on June 4, the NIH may decide to put Mayo on a “high-risk” list that would make grant administration more difficult, as well as leave a black mark on the institution’s reputation.

Poll: Fewer opportunities in 2005 to participate in clinical trials

In 2005, 10% of surveyed adults say they have participated in a clinical trial, down slightly from 11% in 2004, according to a new survey from Harris Interactive. Despite the consistency in participation, 15% of adults say they have had the opportunity to participate, down from 19% the year before. Those who have participated give many reasons for doing so: 36% say they did to earn money, down from 50% in 2004; 19% to get free medication, down from 27%; 30% to get more educated about their health, down from 39%; and 25% because information they read, saw, or heard influenced them, down from 41%.