Where to look for subjects and how to approach them to join

It used to be that patient recruitment was a rudimentary process, wrote Diana Anderson, PhD, founder of subject-recruiting firm D. Anderson & Company in her book *A Guide to Patient Recruitment and Retention,* (Thompson Center Watch, 2004).

Today, individual sites are no longer the only ones in the recruitment game. They have been joined by site management organizations and other pros that have made the recruitment process more sophisticated and competitive. It is consequently more difficult to find and retain qualified candidates for trials.

In fact, Anderson wrote that 81% of studies must extend enrollment periods by one to six months, putting these studies behind schedule before they even begin.

Yet there are ways in which a site can help stack the deck to its advantage and meet subject recruitment goals in today’s competitive environment.

Make participation easy

One would think that subjects balk at the idea of participating in a trial because they might fear...  > p. 2

Prepare for FDA with simulated audits that put you on the spot

Conducting a mock FDA audit on a research study is a critical component of sound business practices for investigators, says Adi Shamoo, PhD, professor and bioethicist for the University of Maryland School of Medicine. (See “Noncompliance News” on pp. 10–11 for more.)

The mock audit can help investigators understand not only the type of questions that auditors might ask, but also how to answer them, says Michael Hamrell, PhD, RAC, president of MORIAH Consultants (www.moriahconsultants.com), whose company helps sites prepare for the scrutiny federal regulators will apply to their research methods.

“Basically, [in a mock audit] we go through the same kinds of questions and issues that the FDA would [during a real audit], so we can check their readiness,” Hamrell says. Audits include interviewing the investigator as well as poring through the records in the same manner FDA investigators would.

View from the outside

It can be beneficial to hire outside experts to conduct a mock audit, says Hamrell. They can give an investigator something the investigator doesn’t have: a fresh look at the work conducted at his or her...  > p. 4
Recruiting

it wouldn't improve their condition, such as could be the case if they receive a placebo rather than the actual drug.

But this is rarely the reason a subject declines to participate. That happens 9% of the time, according to Anderson's book.

More often subjects decide not to sign up for simpler reasons, such as convenience. According to research Anderson quotes, two-thirds of subjects who don't participate in a study say it's because of the research site's location or hours. This may be especially true when it comes to sick subjects. Anderson tells recruiters to ask themselves: Are you taking their needs into consideration? Many studies don't, says Anderson.

**TIP:** Think like a business. If you make your trial more convenient, it will be more attractive to subjects, says Anderson. Structure your hours to mesh with subjects' schedules and focus on offering the same quality service that a bank or retailer offers its patrons.

"Data suggest that study candidates want to be treated like customers and expect good customer service," Anderson wrote.

Although some sites can outsource elements of recruitment to companies specializing taking those first calls, she adds that participants' view of a study "ultimately rests with the investigative site's participation and follow-up with recruitment efforts."

**TIP:** Return calls. It sounds obvious, but not getting enough information about a trial was one reason 12% of subjects gave for not participating in a clinical trial.

Anderson says nearly 25% of prequalified volunteers fail to get into the randomization stage of a trial simply because they had called to ask additional questions before committing and the study organizers didn't return their phone calls quickly enough. Always return calls within three to five days.

**Employ best practices**

The equipment you use must meet certain industry standards. The drugs you're researching are produced according to strict standards. Thus your recruitment efforts must also meet high standards.

Anderson suggests these steps for developing best practices:

1. Write the recruitment policy as a standard operating procedure and include the purpose at the top followed by the task (such as designing a direct mail campaign, patient recruitment call scripts, HIPAA compliance process for recruitment, etc.) as well as the sources of the policy information and, if possible, attach good examples of what you're looking for.

2. Sell the policy to staff not as a series of suggestions that are good ideas to follow, but as mandatory procedures.

3. Create a committee to review them at least annually and solicit its suggestions for improvement.

Sponsors sometimes offer patient recruitment training for their research sites, Anderson points out, so investigators might want to ask whether it's available.

Sponsors not only are interested in helping promote regulatory compliance among their sites, but also "they view this investment as key to enlarging the pool of better trained sites" in general, she writes.

**Reach out to communities**

Some high-tech recruitment firms successfully use scientific tools such as metrics and informatics to help target ad-buying in different metropolitan markets.

Yet the good news for investigators at sites that don't have a big budget for such analysis is that there's no substitute for community outreach.

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Although there are many venues to choose from, look in your back yard for prospective research subjects. Check the following:

- Local and national chapters of professional organizations such as the American Heart Association, American Cancer Society, etc.
- Patient support groups, community centers, and county hospitals
- Mail attractive, professional-looking materials to local physicians and pharmacists and follow them up with phone calls
- Participate in local health fairs
- Sponsor fundraising activities (e.g., breast cancer walks)
- Offer lunch and learn health forums related to the condition or symptoms your study will be treating
- Retirement communities and religious organizations

Consider your community outreach efforts a standing, long-term project—not just a stopgap for this week's recruitment crisis, Anderson writes. In other words, don't stop reaching out once you meet the current enrollment goal. Your efforts can help you in future studies.

**Fast fact:**
**People who do know about trials have a generally positive attitude toward them, despite high profile stories such as the death of Jesse Gelsinger in a 1999 University of Pennsylvania gene therapy trial.**

"Community outreach can be thought of as having short-term and long-range goals," Anderson writes. "Short-term community outreach has the immediate purpose of enhancing patient enrollment for currently ongoing studies.

"Longer-range objectives have the broader intent of educating the public about clinical trials in general, and informing interested parties about where they can find information about specific studies if they seek participation for themselves, or for family and friends."

**Start slow with the basics**

Once prospective subjects answer your advertisement or come to your study via other means, keeping them becomes a priority. Retention begins with the first conversation with the subject, as does the education process.

Anderson says that although negative media coverage about clinical trials might have come up from time to time over the past several years, most prospective participants aren't aware of what a clinical trial is in the first place.

Her company's market research found that the people who do know about trials have a generally positive attitude toward them, despite high-profile stories such as the death of 18-year-old Jesse Gelsinger in a 1999 University of Pennsylvania gene therapy trial.

The lack of knowledge is more of a problem than the bad rap clinical research has gotten with such incidents as the Gelsinger story, Anderson says. To overcome this lack of information, baseline information needs to be sent out during the earliest parts of the recruiting process to explain how a study works and what it can offer.

"When [prospective patients] call in to our call center, we send out information about 'what is a clinical trial?' to begin with, so that people have more information about the whole process," Anderson said in an interview with CTC during the Association of Clinical Research Professionals 2005 annual conference in Orlando, FL, in early May.

"As for the trial itself and the nuances specific to a given trial, that's down the line in terms of explanation. We let the research sites explain those specific aspects."

**Questions? Comments? Ideas?**

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Simulated audit

Site. They may also have insights on the FDA’s current priorities as well as much auditing experience. "Many investigators, over a whole career, might go through two or three audits; I do 20 or 30 a year," Hamrell says, and many auditors perform even more than that. "Once you do a number of these, it gets to the point where there’s nothing you haven’t seen."

But sites can also conduct these audits themselves or use an auditor provided by a sponsor.

Audit traps

Below are more tips to help you get started:

- Conduct a role-playing exercise in which someone acts as the FDA auditor and interviews you about your study. When you answer questions from the interviewer, try to answer only the question without offering any more information than is asked.

Offering too much information can open the door to more questions that may ensnare investigators. This can get investigators into a jam that would have been avoided had they just stuck to answering the question at hand, Hamrell says.

For example, if an investigator were to ask you, "Do you have the time?" most of us would be inclined to glance at the nearest clock or watch and offer the time of day. That, Hamrell points out, is offering more information than, technically was requested. The appropriate answer, if an FDA auditor were asking, would be "yes" or "no."

- Read guidance documents and warning letters posted on the FDA Web site to glean insight into current enforcement priorities and think about how certain regulations will be interpreted, he adds.

"Warning letters tell you what they’ve cited other people for recently," Hamrell says. "An investigator can look at them and say ‘if they came to my site, would they make the same finding?’"

- Read guidance documents, as well, he says, offer a historical view of particular regulations and a context for their interpretation by FDA auditors. Familiarize yourself with new guidance documents—some of which might have come out since you finished work on the study you are auditing.

- Read the "talk papers" and speech transcripts posted at the FDA Web site devoted to clinical research topics, Hamrell advises. Sometimes they, too, offer insight on issues that could come up in your audit.

- Be familiar with your work. Go back through study records and bone up on the data to refresh your memory on the protocol and its execution.

"Go back and look at everything," Hamrell says. "Make sure all your files are there and up to date, and that you can pull all the medical charts, dust them off, and look at them."

Show confidence

The idea of an FDA audit of your clinical research site can be intimidating—especially after you’ve read the past 10 FDA warning letters to clinical investigators just like you.

But it shouldn’t be, Hamrell says. You should know the regulations, you know how things were done when the study took place, and you remember the effort put into dotting the regulatory Is and crossing the Ts.

"If you’re doing good work, and you’re doing it right, you shouldn’t have to worry," Hamrell says. "It’s the natural response of humans to worry, but you shouldn’t have to if you have good documentation practices, well-trained staff, and . . . know what’s going on with all the subjects in their trial."

Survivors of Nazi medical experiments to receive more compensation

Some of the surviving victims of Nazi medical experiments will be paid an additional 2,450 euros, after receiving 4,243 euros in March 2004, reports Reuters. The additional funds will bring the 714 victims’ total compensation to 6,693 euros, or $8,675 each. The funds come from "Remembrance, Responsibility and Future," a foundation set up in 2000 by the German government and industries to compensate victims of the Nazis, says the report.
Ten pointers for new investigators

A top patient recruiter and research contractor outlines what most doctors should understand before signing up to conduct research

Whether it's career advancement, intellectual stimulation, or extra income that drives a physician to make the leap into clinical research, there's no denying that the more well-informed a doctor is before jumping into the field, the more likely he or she is to succeed, says Diana Anderson, PhD, founder of patient-recruiting firm D. Anderson & Company as well as the contract research organization RRI.

Don't think of research as easy money, Anderson advises physicians during a presentation she developed for prospective and new investigators. Researchers are under constant deadline pressure and have considerable regulatory obligations that cannot be delegated. Research takes time away from a doctor's regular practice.

If this doesn't sound like something you can handle, maybe clinical research isn't for you, says Anderson.

Prospective investigators should view research as emotionally rewarding. Investigators help develop better and safer medications for their patients. They participate in developing cutting-edge treatments unavailable to their peers. They secure state-of-the-art medications and devices for some patients who otherwise would not be able to afford them. But research can also bring more tangible benefits, both financial and professional.

For example, physicians may be able to network their way into professional circles that previously may have been closed to them. They get work published in peer-reviewed journals. Some investigators who can manage their research well can even earn extra income.

For those who are intent on making the leap, Anderson offers the following tips on how to figure out where—and how well—you and your practice fit into the world of clinical research:

1. **Consider a Phase IV study first.**

Post-approval studies typically are more simply structured than preapproval studies, if for no other reason than that they usually don't need a control group. These can make good tests for a physician to determine whether he or she wants to join more difficult protocols down the road.

2. **Know where investigators fail.**

Where are they most likely to make mistakes? Often it's because they fail to keep adequate and accurate records, execute deficient informed consents, don't follow protocol, fail to report adverse event, and improperly account for experimental drug/device disposition. Plan in advance to pay special attention to these problem processes.

3. **Understand all of your regulatory responsibilities.**

It's a must: Before the study begins, an investigator must understand the processes and paperwork involved in its execution and plan to make sure everything is covered. During the study, know when and how adverse event reporting must take place; and after the study, know what happens during a site or sponsor audit.

4. **Understand staff requirements.**

Good research staff begin go hand in hand with a good clinical coordinator who knows and understand the FDA's Good Clinical Practices and is obsessive about following the study protocol, maintaining perfect source documents, and filling out case report forms perfectly, says Anderson.

5. **Plan for space requirements.**

Records and patients take up space. So do new staff, such as your study

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Clinical Trials Compliance—June 2005 © 2005 HCPro, Inc.
New investigator  < p. 9

coordinator, finance manager, and, if you still need to hire them, nursing and clerical staff. Have a plan to accommodate the physical space that clinical research requires.

6. Plan for the financial aspects.
In short, who is assuming liability and risks inherent therein? Who's indemnified? Understand what you're on the hook for. Further, understand how to put together a study budget and how to manage cash flow—or how to delegate it to someone who does.

7. Be prepared to lose money in the first year of operation.
To get quality results from a research staff, you have to recruit them just as you recruit patients. And you must pay them, too. "You can't invest after you make the money in this industry," Anderson says.

8. Be prepared to break even financially after that initial loss.
On paper, most well-run research sites show a profit of about 12% once they are established. Unfortunately, hidden costs, such as preparing for and attending IRB meetings, study supervision, and adverse-event management, cut into an investigator's time and income.

9. Gun for enrollment.
If you're not at least striving to be the best-enrolled site in a multisite study, then stay out of a study, Anderson says. You have to have both means to identify and recruit patients from within your practice as well as the talent and wherewithal from somewhere on your team to recruit patients from outside your practice if necessary.

10. Note which drugs are currently under development.
Did you know that cardiovascular, central nervous system, and anti-infection drugs represented about two-thirds of all pharmaceutical sales in 2001? These are the least likely to be orphaned or developed but not well prescribed.

Anderson says the go-getter investigators also understand that business development is a core competency they need to learn in order to successfully manage sites that make money and deliver information on time.

It will also help them establish and start a pipeline that brings bigger and better research work.

Does it sound like getting into the clinical research field is a big undertaking? It is, but that doesn't mean you should sit on the sidelines.

Anderson points out that although there already are 50,000 investigators in the United States, only half of them will perform more than one study. Looking at the current annual growth rate of multisite studies every year, that projects to a need for 380,000 new PIs by 2013. This presents many opportunities for those willing to embrace them.

FDA critics speak out against clinical trials proposal

Critics are speaking out against an FDA proposal that states international guidelines designed to protect patients do not have to apply to clinical trials conducted abroad, reports Reuters. The guidelines in the Declaration of Helsinki guarantee patients in clinical studies continued access to drugs at the end of the trial and places limits on the use of placebos in developing countries.

Though the FDA currently complies with the guidelines, proposals, made in 2004, would only require trials to comply with Good Clinical Practices. Critics from organizations such as consumer group Public Citizen say this adds to the growing trend of "U.S. exceptionalism," says the report.
An oldy but a goodie: OHRP celebrates the *Belmont Report*, makes oral histories and DVDs available

To commemorate the 25th anniversary of the *Belmont Report*—the bedrock upon which modern bioethics standards and regulations are built—the HHS’ Office of Human Research Protections (OHRP) has included transcripts of interviews with many of the principals involved in writing the document on its Web site.

Why does a report created in 1979 by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research matter today? Simply put, says OHRP senior public-relations coordinator Patricia El-Hinnawy, this is interesting stuff—not only for historians, but for current researchers who want to know how the field has arrived at its current thinking on ethics as well as those active in the human subject protection community.

IRB members can also use it, she points out, to more deeply understand the logic behind ethical principles and help guide them through their decision-making processes.

**Oral History**

"I did not anticipate that the report would have such longstanding status, or have such wide repercussions," said Donald Seldin, MD, one of the commissioners of the *Belmont Report* group, interviewed for the project by current OHRP director Bernard A. Schwetz, DVM, PhD. "It was simply a summary of the various thoughts, ideas, principles that had governed the Commission for its three or four years in session."

El-Hinnawy, who helped conduct some of the interviews with *Belmont Report* authors, said she was particularly moved when she spoke with Dorothy Height, PhD, chair of the executive committee of the National Council of Negro Women, who sat on the commission.

Height, a civil-rights activist and a friend of Eleanor Roosevelt's was one of the public's representatives on the Commission. Height witnessed the evolution of modern medical ethics firsthand and, through the *Belmont Report*, made her own contribution to the process.

Height said during the interview posted on the OHRP Web site that she would phone other commission members between meetings and discuss matters of justice and beneficence in research as they formulated how to most fairly treat vulnerable subject populations such as prisoners and pregnant women.

"I think . . . the report is very clear about the respect for human personality, and I think it is very clear about something that I think the general public often doesn't understand as we talk about equality," Height said. "I think it rightfully put the concept of equality within the basis of the needs in the situation rather than just say that equality meant just being equal."

**DVDs free for the asking**

Because the *Belmont Report* and the principles it espouses comprise a "101 course" for clinical investigators today, OHRP posted transcripts such as that of Height's on its Web site. It is also offering video or DVD versions of the interviews, which will be sent at no cost to those who request them. In addition to the interviews, the entire 67-minute 25th-anniversary program about the *Belmont Report* is available on video or DVD as is an abbreviated nine-minute presentation.

El-Hinnawy said the materials are especially appropriate for new investigators or newly appointed IRB members struggling to get up to speed on research ethics.

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**Fast fact:**

The *Belmont Report* got its name from the buildings in which the commission that wrote it first convened from 1974–78.

"Just as there are all kinds of learning styles, we have tried to present a variety of ways for people to access this information," El-Hinnawy said. "That's . . . why we included the nine-minute video for that group who's pressed for time or intimidated by larger bodies of knowledge in an area that they're just approaching for the first time."
News in brief

Despite ethics debate, NIH AIDS study valid

An Institute of Medicine Panel concluded that the results of research in Uganda to test the AIDS medication nevirapine is valid, despite lapses in correct investigational procedures, reports the Associated Press.

The National Institutes of Health study concluded that the drug was safe to protect babies from AIDS. Though the study had flawed document keeping and unreported adverse events, the panel found that the lapses did not affect the outcome, says the report.

Deal okays Cuba to use Malaysians in clinical trials

Malaysians will be used in clinical trials for Cuban vaccines as part of an agreement to increase bilateral trade, reports Agence France-Presse. Cuban officials said Malaysia’s multiracial and diverse population makes it ideal for testing their pharmaceutical and vaccine products.

The two countries will partner in biotech research and development and the use of Malaysians in trials was part of the deal with Cuba for procurement, manufacturing, and research of vaccines and drugs, says the report.

U.S. formally probing Tysabri withdrawal

Biogen Idec, who makes Tysabri® along with Elan, confirmed that the U.S. Securities and Exchange Commission has started a formal investigation in the drug’s withdrawal, reports Bloomberg.

The commission is investigating whether any violations of federal securities laws occurred in the market suspension of Tysabri, says the report. The drug was withdrawn February 28.

Lilly halts Xigris pediatric trial

Eli Lilly has halted enrollment in its clinical trial for the drug Xigris in pediatric patients with severe sepsis, the pharmaceutical company reports. Patients taking Xigris did show improvement over those on placebo.

Additionally, more children treated with Xigris experienced central nervous system bleeding than those given a placebo: Four of the patients got intracranial hemorrhages while being treated with Xigris, compared with one taking a placebo, reports Reuters.

Xigris is not indicated for use in pediatric severe sepsis, but is approved for reduction of mortality in adult patients with severe sepsis, according to Lilly.

Patients sue Amgen for clinical trial drug

Two Parkinson’s patients in a discontinued clinical trial are suing the pharmaceutical company Amgen because they want to continue receiving the experimental treatment, according to the New York Times.

Although Amgen halted the study and says the drug in ineffective and may be dangerous, the patients contend the drug helped them and that Amgen is violating a moral and legal obligation to continue supplying the drug.
Ask the expert: How should you reply if your site gets hit with a Form 483 from FDA inspectors?

This month’s experts are Christie Morgan, CCRC, managing director of clinical research for Newton-Wellesley in Newton, MA; Robert Nicholas, JD, partner at McDermott, Will, & Emery; and Sandra Vose, MBA, head of global monitoring for Covance Inc.’s Late Stage Development Services. Together they wrote Clinical Trials Roadmap for Physician Practices, published in January by HCPro, Inc.

Q: If FDA inspectors file a Form 483 outlining compliance observations and list problems, how should I reply to it?

A: Although you are not obligated to do so, you should reply to the 483 within three weeks. The reply should discuss in detail how you intend to address any deficiencies. Ordinarily, if an organization adopts new procedures or provides staff training, it will address the specific problem and reduce the possibility of recurrence. Also, if you can correct an observation after the fact, do so. A reply to the 483 often is sufficient to end a matter. However, the FDA may send follow-up correspondence seeking further clarification.

Your reply to the FDA should address the FDA’s concerns. You may also dispute an observation that is not accurate or is not a violation of the FDA’s regulations. But don’t act defensive, sound argumentative, or raise frivolous or minor objections to the FDA’s observations.

The FDA is looking at your reply for several purposes, including the following:

- To see that you understand the FDA’s specific regulatory requirements and appreciate the seriousness of the requirements
- That you are undertaking corrective action to resolve the observation regarding the study audited, if corrective action is appropriate
- That you have taken corrective action to reduce the possibility that a similar problem will occur in the future

Your reply to the FDA should be honest and realistic. Replies to a 483 should be sent to the inspector and the FDA district office unless the inspector tells you otherwise.

Review your clinical trials agreement (CTA) to determine whether you are required to notify the study sponsor about the 483. The sponsor can assist you with your reply to the FDA, although typically neither the FDA nor CTA will require that step. However, even if you take advice from the sponsor, you are personally responsible for the accuracy and completeness of your reply and any corrective action commitments you make to the FDA.

Determine whether a 483 (for an ongoing study) should be submitted to the IRB based on the IRB’s reporting requirements.

Q: What should I do if I receive a warning letter from the FDA in the wake of a 483?

A: Warning letters are issued when the observations in the 483 and the establishment inspection report (EIR) are serious/extensive or where significant safety concerns are presented. A warning letter may be issued even if the reply to the 483 was acceptable. It will contain the more significant inspectional observations as noncompliance matters and may also contain additional compliance items from the EIR.

Although a reply to a 483 is not required (but is advised), you are required to respond to a warning letter, ordinarily within 15-30 days. The reply to the warning letter should follow the same guidelines as those for a 483 reply. However, because this is more serious, seek the assistance of an experienced regulatory consultant or lawyer to address the intended observations.

In cases of extensive or deliberate noncompliance with 21 CFR Parts 50, 56, 312, and/or 812—particularly if the FDA concludes that a PI is unwilling to comply or incapable of compliance—and in cases of fraud or other similar misconduct, the FDA may seek to disqualify a PI from conducting future FDA-regulated clinical research.

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Expert

When the FDA seeks to disqualify a PI, it isn’t an automatic process. The agency offers PIs informal conferences that allow them to defend their work and avoid disqualification. If the PI in question doesn’t convince the FDA that he or she should not be disqualified, the FDA provides an opportunity for the person to step down voluntarily.

The written offer is posted on the FDA’s Web site (www.fda.gov).

Noncompliance news

Financial disclosure issues, informed consent, records storage at issue in FDA warning letters

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 March 2 and April 11 to device research sites in Illinois and Florida.

The FDA sent a warning letter to Lowell S. Weil Sr., DPM of the Well Foot & Ankle Institute in Des Plaines, IL. Included among many regulatory problems inspectors found were the following:

☑ Five subjects did not sign informed consent forms until after they had been treated with the study’s investigational device
☑ Two subjects had not signed informed consent at all
☑ Twenty-two subjects—all listed individually, (unusual in a warning letter)—who should have been excluded from the study were treated with the investigational device

The FDA also found the investigator’s responses to these problems to be “inadequate” in all cases. The investigator blamed staff for the errors pointing a finger at a nurse who left the investigator’s employment during the course of the study.

Yet the nurse wasn’t the only person at fault, FDA inspectors noted, because “it appears that a number of different people entered data onto the [case report] forms, as evidenced by the variety of handwriting styles used.”

This warning letter offers several key lessons to investigators who want to avoid similar problems with their research, says Adil Shamoo, PhD, professor and bioethicist for the University of Maryland School of Medicine.

First off, he says, investigators who make mistakes fare better when they take responsibility for problems found in FDA inspections rather than pointing the finger, as was done in this case. In their written responses to inspections, sites should outline how they will fix problems so that they don’t happen again. While taking a proactive stance doesn’t guarantee that will get investigators out of the doghouse, it does give them a better shot at resolving the issue with the FDA. “According to Shamoo you’re supposed to say,

☑ These were errors. We will take corrective action
☑ We will inform those patients that this was done
☑ We will apologize
☑ We have instituted quality assurance means, moni-
toring means, and education and training to prevent this from happening again.

The other lesson that this letter teaches is that FDA inspectors are detail-oriented. Inspectors watch for inconsistencies in case reports and other forms. The different handwriting used in this instance threw up a red flag.

"Auditors look at the type of pens and pencils used for example, if all the signatures are in the same pen for the informed consent, there's no way in the span of a month's recruiting of subjects that they all use the same pen," Shamoo says. "The key to it is dates and signatures—do they all look alike? This is how auditors catch these things."

At the end of the letter, the FDA requests to see the corrective plan the site will take to fix the violations inspectors noted, which is a traditional component of most warning letters. In this instance, the agency follows that with an unusual request to see "a complete list of all clinical trials in which you have participated for the last five years, including the name of the study and test article, the name of the sponsor, the number of subjects enrolled, and the current status of the study."

Shamoo says the FDA might have made that request because of the contradictory answers the investigator offered in this instance. The agency is probably concerned that these problems weren't limited to this particular trial, he says.

Another warning letter sent to a Venice, FL device investigator revolved around records that had been sent to a storage facility and not made available to FDA inspectors.

This can happen, Shamoo says, when inspectors show up a few years after a site completes its part in a research study. "[Sites] should do a dry run for an FDA audit every now and then, as part of their good business practices." Shamoo says. "Because you never know when [FDA inspectors] might show up.

Sometimes they tell you, sometimes they don't."

Although it might be tempting to warehouse records to get them out of the way, he says, be aware that the FDA can come calling long after a study is completed.

In the case of the Florida researcher, the investigator was obligated under its sponsor agreement to notify the sponsor if records—including informed consent forms, case reports, and other patient documents—were disposed of or moved. The site failed to meet this obligation, a point that was noted by FDA inspectors. Further, the site couldn't produce the financial disclosure information it had filed with the IRB at the outset of the study. In fact, it was questioned whether this disclosure information was filed at all.

Problems like the ones the Florida investigator encountered are easy, "checklist stuff" that most investigators can avoid by getting a plan down on paper and following it.

Problems arise when an investigator fails to write this information down and instead of attempts to recall details by memory and lets some information fall through the cracks, says Shamoo.

Although this might be just a simple case of poor recordkeeping, Shamoo said, the FDA obviously determined that the regulatory breach it represented was serious enough to issue a warning letter about it.

"Sometimes people work from memory, and [this investigator] probably just didn't remember what the protocol said," Shamoo says. "It's a mistake, for sure, and it could have been avoided with better communication between sponsor and investigator."

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**Clinical trials linked with cancer survival rates**

Older teens and young adults are less likely to participate in clinical trials, which may result in lower survival rates for some cancers in these age groups, suggests new research published in the May 1 issue of Cancer. Although cancer survival has increased overall in the past 25 years, there has been little improvement for those ages 15 to 45, according to HealthDay News. Researchers at M.D. Anderson Cancer Center in Houston found a correlation between age-survival rates for people with most sarcoma cancers clinical trial participations rates.

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**Correction**

Christie Morgan is the Managing Director of Clinical Research for Pediatric Health Care at Newton-Wellesley, Newton, MA, which is a private practice, not Newton-Wellesley Hospital as has been indicated in past articles. We regret the error.

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FDA updates guidance on premarket software/ firmware for research

On May 11, the FDA updated its guidance for researchers submitting notifications that they will be testing computer software and electronic devices. The guidance document specifically addresses safety of both computer software applications and firmware—programs that run the device itself.

In the guidance, the FDA recommends that device makers state in their document submissions whether the device has a major, moderate, or minor level of concern determined by the level of risk of injury to patients. FDA defines levels of concern in the following ways:

**Major:** We believe the level of concern is Major if a failure or latent flaw could directly result in death or serious injury to the patient or operator. The level of concern is also Major if a failure or latent flaw could indirectly result in death or serious injury of the patient or operator through incorrect or delayed information or through the action of a care provider.

**Moderate:** We believe the level of concern is Moderate if a failure or latent design flaw could directly result in minor injury to the patient or operator. The level of concern is also Moderate if a failure or latent flaw could indirectly result in minor injury to the patient or operator through incorrect or delayed information or through the action of a care provider.

**Minor:** We believe the level of concern is Minor if failures or latent design flaws are unlikely to cause any injury to the patient or operator.

The level of documentation the agency requires should follow the device maker's stated level of concern—which the guidance underscores is unrelated to the FDA's Class I, II, and III classifications referred to in other regulations, as well as a researcher's risk analysis. Read the full guidance at [www.fda.gov/cdrh/ode/guidance/337.html](http://www.fda.gov/cdrh/ode/guidance/337.html).