IRBs: How to proceed with emergency research

IRBs around the country have been asked to approve an atypical trial in recent months—one that proceeds without getting informed consent from subjects. The trial involves administering PolyHeme, a blood substitute to trauma patients who are in transit to the hospital.

Because their condition makes them unable to communicate, it is impossible for subjects to give their consent to participate, and there may not be time to get the approval of a relative.

This research falls into an unusual category. Its sponsor applied for a special investigational new drug exemption (IND) under 21 CFR 50.24, which allows the trials to proceed without getting informed consent from the subjects.

This type of trial is rare, says Paul Goebel Jr., CIP, vice president of Chesapeake Research Review, Inc., in Columbia, MD. “The reason it’s not very common is because the regulatory burden is so high,” he says. However, your IRB may one day be asked to review this type of trial or a similar one that is exempt from key regulations.

The following is an outline of the regulations that may apply to these so-called emergency trials. Understanding the requirements can help your board proceed appropriately when confronted with unusual requests.

The first type of trial that you may face is one such as the PolyHeme trial, which is covered by the federal regulation 21 CFR 50.24. Because it is important for the FDA to agree to this type of study, the sponsor must send a separate IND or investigational device exemption (IDE) to the FDA, which allows it to waive the informed consent process. A waiver is required in these cases because there is no other

Tips for successfully negotiating a study budget with a sponsor

In the past, pharmaceutical companies were less concerned about the amount of money spent on clinical trials, so individual sites rarely had to worry about payments coming up short.

However, now most sponsors monitor the bottom line much more carefully. Their goal is often to run trials at the lowest possible cost. This means that individual sites must be increasingly vigilant to ensure that all research-related costs are covered and that the trial isn’t going to leave the organization in the red.

There are some steps you can take to ensure that you don’t get stuck in a money-losing venture, says J.T. Matthews, RRT, MBA, director of the clinical trials office at the Stokes Research Institute at the Children’s Hospital of Philadelphia.

The first and most critical of those steps is to understand and detail your own costs. If you don’t know what it costs to prepare an IRB submission, or to conduct a chest x-ray, you will have little chance of knowing whether the sponsor’s reimbursement will cover those costs, says Matthews.

Children’s Hospital has developed a standardized price list for the entire organization. This not only ensures consistency, but
legal means of conducting the trial. The majority of these trials will be conducted in academic medical centers, most often in the affiliated hospital or emergency room, says Goebel.

The regulatory requirements are very stringent with regard to these trials, he says. A trial must meet each of the following criteria to qualify for a waiver:

☑️ It involves a life-threatening situation.

☑️ Existing treatments for the condition must be unproven or unsatisfactory.

☑️ Collection of valid scientific evidence is necessary to show whether the proposed treatment is safe and effective.

☑️ Informed consent is not feasible because the subject is not in a position to give consent and there is no time to get authorization from a legally authorized representative.

☑️ There is no practical way to prospectively identify an eligible subject.

☑️ Participation holds out the prospect of direct benefit to the subject.

☑️ The trial could not be conducted without the waiver.

☑️ The risks are reasonable considering what is known about the standard therapy and the research intervention.

☑️ A data monitoring committee (DMC) (i.e., an independent scientific board), must be established to measure the progress as the study proceeds. The DMC recommends whether to continue the study, modify it, or end it, either because the results are so good that everyone should receive the research intervention, or because they are so bad that the study should be stopped.

It is the sponsor’s job to explain and document these points to the FDA. The IRB must review the information to ensure that all points are met, both before the start of the trial and throughout its course.

“In this case, the IRB’s role is pretty well defined. There are certain judgments that the IRB has to make,” says Goebel.

One of those judgments is whether the risks of the trial are reasonable in relation to what’s known about the medical condition, says Goebel. Therefore, IRB members must be educated about the disease or condition in question or must hire an expert consultant who is, says Goebel.

The IRB is also responsible for ensuring that the
public is made aware of the research and that the leaders in the community have an opportunity to comment on the plan. The FDA has issued guidance on how to proceed with regard to this public notice, says Goebel.

A solid means of informing the public about the trial is through television coverage. This coverage include news broadcasts, public service announcements, and news interviews of the study physicians or others knowledgeable about the study, says Goebel.

It’s also critical for the IRB to take public sentiment into account when deciding whether the trial should continue. If public reaction is negative, it may mean that more education is required or that the trial is not appropriate and should not move forward in that locality, he says.

In the PolyHeme trial, IRBs have scheduled public meetings to spread the word out about the research and ensure that the trial has been given sufficient coverage. The Duke University IRB even required that the public be given a means of opting out of the trial if anyone was concerned about becoming a participant.

The IRB had hosted a series of poorly attended public meetings and decided to expand its efforts. Currently, those who do not want to be enrolled can put themselves on a do-not-test list and wear a blue bracelet, so that they are identified as nonparticipants.

Goebel says the IRB’s role should not end once the subject has been enrolled in the trial. It should ensure that the subject completes an informed consent process as soon as he or she is able. The subject must have the ability to opt out at this point or to continue participating in the trial. If the subject drops out, the existing data may be retained, but no future data may be collected, says Goebel.

The IRB is responsible for ensuring that the public is made aware of the research and that the leaders in the community have an opportunity to comment on the plan.

The subject is in a life-threatening situation that necessitates the use of the test article

Informed consent cannot be obtained

Time is not sufficient to obtain consent from a legal representative

There is no available alternative method that provides an equal or greater likelihood of saving the subject’s life.

The physician is also required to obtain an opinion from a second physician to confirm his or her contention that use meets all four conditions, says Goebel. This provision has been used much less frequently since the 21 CFR 50.24 was put in place, says Goebel.

Research without IRB approval

There is another provision in the regulations that allows research to continue without IRB review during an emergency situation.

This case also applies to life-threatening, emergency situations. It allows a physician to administer an experimental treatment without IRB approval, provided that the intervention is reported to the IRB within five days.

In order to use this provision, there must be no standard acceptable treatment available and the life-threatening condition could lead to death if not treated promptly.

Because of time constraints, the intervention must be started before IRB approval can be obtained.

This scenario is unlikely to occur, however there may be rare cases when this situation may arise, says Goebel.
also gives budget negotiators a quick reference tool to access when developing a study budget analysis.

It's critical for organizations to break down the budget proposed by the sponsor and itemize their own costs line by line, says Matthews. Then they can determine how much it will cost to perform the trial and that number can be compared to the reimbursement that will be provided by the sponsor. This figure becomes the starting point for your negotiations.

Although this step may seem simple and obvious, it is, surprisingly, not something that all sites do, says Matthews.

**Experience is key in negotiations**

When it comes to actually negotiating the budget, experience can be key. At Children's Hospital, the clinical trials office offers to analyze and negotiate study budgets for investigators—a service that many use, says Matthews. This ensures that people with the most budgeting and negotiating experience are working to ensure all costs are covered.

In the past, individual physician investigators would negotiate his or her own study budgets, but they weren’t always prepared for the complexity of the task.

“They don’t have budget training in medical school,” says Matthews, and the investigator’s experience is often limited by the number of budgets they worked on. For example, an individual investigator might only negotiate four or five budgets in a given year, whereas the clinical trials office negotiates more than 100 budgets annually, which gives its employees critical experience.

“Right now it’s an optional service,” says Matthews. “We’ve never forced our investigators to use our budgeting and negotiation services, but [they have] plenty of benefits.”

The experience of handling multiple negotiations comes in handy when working with the various sponsors. “What works for some organizations will not work for others,” says Matthews. Even within one sponsor organization you may find variations, he says. For example, when working on a cardiology trial, the cost of a chest x-ray may be approved by the sponsor without issue, but that same x-ray cost may be rejected by the same sponsor’s oncology department as being too costly.

“I think a lot of it has to do with knowing who your customer is,” says Matthews.

**Standardizing the budget process**

When working with five different sponsors, you’re likely to run into five different methods of structuring a study budget. But your organization should take steps to standardize its own processes to cut down on confusion, says Matthews. At Children’s Hospital, budget planning follows a similar format. The costs are broken down the same way, regardless of how the sponsor wants the information structured. Once the budget analysis is complete, the information is restructured to meet the sponsor’s requirements, says Matthews. He says a future goal should be for the industry to standardize its budget process to cut down on confusion.

**Recognizing the sponsor’s needs**

It’s also important to understand that you may not get everything you need out of the negotiations. “Negotiation is really a back-and-forth issue; it’s not a one-sided deal,” says Matthews. When going into a negotiation, you need to be willing to grant concessions to the sponsor, not just fight for your own issues, he says.

“You need to come out with a win-win situation. You can’t expect all of your issues to be covered,” says Matthews.

By the same token, you can’t back down if you know that your costs are legitimate, he says.

You might hear things such as, “you’re the most expensive of all my sites,” or “out of all my sites, you’re the only one asking for this,” says Matthews. “When you go to a budgeting seminar, everyone laughs about this. Everyone gets told the same thing.”
Although sponsors are monitoring the high costs of some sites, “they should also be wary of the low-cost provider. Why are their costs so low compared to everyone else’s?” Matthews asks. This could be a sign that this research organization might be tempted to cut corners so that it doesn’t end up with a shortfall.

**Saying no to a trial**

If your costs are legitimate, it’s important to persist or realize when it’s time to walk away.

“Sometimes the expectations are too high, or the finances are too low,” says Matthews. “While I might have an investigator who wants to do a certain project, we might have to recommend that they say no.”

“No institution goes into a negotiation planning for a loss, and I am sure we have unknowingly accepted some inferior budgets,” says Matthews. “But as a not-for-profit organization, we cannot accept a loss when the trial involves a for-profit pharmaceutical organization.” A not-for-profit should not be subsidizing a for-profit company, he adds.

**Enrollment issues**

Some sponsor organizations will be more willing to meet higher price demands if they are confident that the site can enroll the specified number of subjects, says Matthews. But take care when committing to certain enrollment numbers. The majority of sites are not able to enroll the number of subjects that are needed for a given trial. If the trial winds up short, it can affect the budget and cause the research organization to suffer a loss.

**Payment milestones**

Remember that your vigilance shouldn’t end when the trial is complete. It’s important to ensure not only that all costs are covered, but also that all payments are received. Sponsors often don’t want to give research organizations a lump sum of money per subject because subjects often opt out of trials before they are complete. Therefore, the sponsor might offer the following payment milestones:

- 20% of the costs when the subject is enrolled
- 20% when the subject reaches the halfway point
- 20% when the subject completes the trial
- 20% when the data is complete

When money is coming in gradually, it becomes very difficult to track. Compounding the problem is the fact that many organizations have multiple, sometimes hundreds of trials ongoing at once. It’s critical to develop a system to track these dollars, says Matthews. Currently, Children’s Hospital has developed its own computer system to help track payments, but it is looking into purchasing a software system to help it meet this need.

**European poll shows mixed reaction to participation in clinical trials**

A poll of 2,300 Europeans determined that 71% of people were unaware of existing protections for human subjects involved in clinical trials, according to the *Pharma Marketletter*. After being told about safety measures in place, 42% of those polled said they would be more likely to participate in a trial. In total, 68% said they would consider taking part in research. The majority of those people (69%) said they would do so to “advance medicine/science.” But a consider-

**Couple sues HMO for failure to cover ‘investigational’ cancer treatment**

The parents of eight-year-old cancer patient Michaela Mease are suing their HMO, HealthGuard of Lancaster, Inc., because it declined payment for a treatment it considers experimental.

> p. 6
according to the *Intelligencer Journal* in Lancaster, PA. The drug in question is MIGB, which is used to treat neuroblastoma, a rare form of cancer. Because the drug is useful in only a small target population and has limited moneymaking potential, no drug companies have decided to pick up the drug. Therefore, it remains an investigational new drug to be used in the context of clinical trials—despite the fact that physicians say its efficacy is well established and that the drug has been in use for more than two decades, the *Intelligencer* reported. “They are denying the claim because they say the treatment is investigational, but it is clear that the only way that any child with neuroblastoma will get this treatment is through a clinical trial,” the family’s attorney, Jack Robinson of Blakinger Byler & Thomas, told the *Intelligencer*.

**Psychology trials may scrap the term ‘subjects’**

The American Psychological Association has issued new guidelines that call on investigators to swap the word “subject” for “participant” when it comes to people involved in psychology experiments, *The New York Times* reported. Association officials said the word “subject” is too impersonal, adding that calling these individuals participants better describes the consensual nature of the arrangement between investigators and those enrolled in the trial, according to the *Times*. However, in cases when the individual in the trial did not officially give consent, such as children, the association recommends that the term “subject” be switched with the word “individual.” Although the decision has supporters, it has also drawn its share of ridicule, including an editorial in a professional journal, according to the *Times*. ■

**AAHRPP releases tip sheets to help organizations meet accreditation standards and stay compliant**

The Association for the Accreditation of Human Research Protection Programs, Inc. (AAHRPP) has released a series of tip sheets designed to help organizations write policies and procedures that meet its accreditation standards, according to its Web site, www.aahrpp.org.

The tip sheets are designed to work in conjunction with the accreditor’s evaluation instrument, which assesses human research protection programs. However, they may also be useful tools for organizations that are looking to improve their research programs but aren’t seeking accreditation.

Tip sheets that cover the following areas are available (see p. 7 for a sample tip sheet):

- Determining whether an activity is human research and therefore is subject to federal regulations
- Evaluating provisions of privacy interests of research participants and confidentiality of data in proposed research
- Evaluating provisions for monitoring data and safety in proposed research
- Exemptions: Determinations and review
- Investigators’ financial conflicts of interest
- IRB authority and independence
- IRB member and IRB consultant conflicting interests
- Noncompliance with human research protection program requirements
- Reporting of unanticipated problems, terminations, suspensions, and noncompliance
- Suspensions and terminations of previously approved research
- Unanticipated problems involving risks to participants or others ■
Sample AAHRPP tip sheet

IRB member and IRB consultant conflicting interests

Related accreditation elements: II.1.C

Federal regulations prohibit IRB members from participating in the review of a protocol in which they have a conflicting interest, except to provide information requested by the IRB. Implementation of this process requires defining, identifying, and acting upon IRB member conflicting interests. Such procedures should also be applied to consultants.

Recommended content:

Define the circumstances under which an IRB member or consultant is considered to have a conflicting interest:
1. Include in the definition interests of IRB members and their immediate families.
2. Define immediate family.
3. Write a definition sufficiently stringent so an IRB member with the same financial interest as an investigator would trigger consideration by the IRB.
4. Include financial and nonfinancial criteria in the definition. Ask if the member or consult is:
   - is a member of the research team?
   - has a financial interest in the research with value that cannot be readily determined?
   - has a financial interest in the research with value that exceeds a specified monetary threshold?
   - has received or will receive compensation with value that may be affected by the outcome of the study?
   - has a proprietary interest in the research, such as a patent, trademark, copyright, or licensing agreement?
   - has received payments from the sponsor that exceed a specified monetary threshold in the past year?
   - is an executive or director of the agency or company sponsoring the research?
   - has an interest that the IRB member believes conflicts with his or her ability to objectively review a protocol?
5. Include additional criteria relevant to the local context.

Describe how conflicting interests are identified:
1. For IRB members:
   Describe the process for identifying conflicts of interest for each type of review conducted by the IRB.
2. For consultants:
   Describe the process for identifying conflicts of interest when a consultant is asked to review a protocol.

Describe the actions taken when an IRB member declares a conflicting interest:
1. Describe the circumstances under which an IRB member with a conflicting interest may be in the meeting room to provide information requested by the IRB.
2. Indicate that an IRB member with a conflicting interest will be asked to leave the meeting room before final discussion and voting.
3. Describe how the actions taken in response to an IRB member with a conflicting interest are documented.

Describe the actions taken when a consultant declares a conflicting interest:
1. Describe the circumstances under which a consultant with a conflicting interest may provide information to the IRB.
2. Describe how the actions taken in response to a consultant’s conflicting interest are documented.

Other suggestions:
1. In policies and procedures for writing IRB minutes, indicate that the name of the person with a conflicting interest must be recorded for each applicable vote.
2. In policies and procedures for writing IRB minutes, indicate that IRB members with conflicting interests cannot count toward quorum.

Source: Adapted from the AAHRPP. Reprinted with permission.
Quick tip: Ensuring proper informed consent

Informed consent is one of the most coveted rights in healthcare. Researchers have long debated how to obtain informed consent from prospective participants. The Belmont Report defines informed consent as informed, understood, and voluntary. The federal rules for informed consent are outlined in 45 CFR Part 46.116 and 50 CFR Parts 20-27.

The informed-consent document must include all relevant information about the study in language that is understandable to the “reasonable” study participant. Some investigators interpret this rule to mean that facilities should write the form in language understandable to a child of six to eight years old.

Also, because research participants may be native English speakers, facilities should translate forms to the commonly spoken languages in their geographic area.

Although the informed-consent document is a useful tool for delivering informed consent to potential subjects, it is merely a tool. Informed consent is a process. The process includes a variety of tools, including subject-recruitment materials (e.g., advertising/marketing materials), verbal instructions delivered to subjects’ families (which may need to be translated for study participants) written materials, and question-and-answer sessions. The process must also clearly state that the subject’s signature documents his or her agreement to volunteer for the study.

The form signed by the potential subject serves as documentation that the consent was “informed,” as defined by the Belmont Report. But how can facilities measure “comprehension” and “volunteerism”? Many individuals were brought up to consider physicians to be somewhere between an “angel” and “God.” As such, they will do whatever their physicians recommend.

Moreover, when individuals are sick, they feel vulnerable and might latch on to any treatment that may cure them or alleviate their symptoms. In cases where an individual has a serious illness and possibly faces imminent death, it is hard to imagine what is going through the individual’s head—much less whether they completely understand the protocol explained by the physicians.

Therefore, it is important for investigators and study sites to use diligence to ensure that their subjects truly understand what they are getting involved with. One way to accomplish this goal is to monitor the informed-consent process.

Recruitment methods for study participants

In some ways, informed consent begins with the investigator’s recruitment methods. Common recruitment methods include formal referrals, informal word of mouth, health workshops and fairs, screenings, the Internet, direct advertising, community meeting places, and chart/record reviews.

Direct advertising is another common mode of recruitment. It includes flyers, posters, newspaper ads, press releases, television spots, radio ads, and Web sites. IRBs must review direct advertising for form, content, and mode of communication. It must not state or imply favorable outcomes, be coercive, use undue pressure, mislead subjects, or use claims of safety, efficacy, equivalence, or superiority.

The research community is hotly contesting recruitment payments to subjects. Government investigators carefully scrutinize these payments, so facilities must carefully consider them as well. IRBs must approve all payment strategies, and the amount of the payment must not be an undue inducement for a candidate to participate.

Investigators commonly inform potential subjects that the facility will reimburse their reasonable costs of participation (e.g., parking, lunch, transportation costs, etc.) and facilities that reimburse subjects in this way should do so when the individual incurs the expenses—the government may consider a lump-sum payment to be suspicious.

Editor’s note: The tip above is an excerpt from the HCPro’s new book Patient Safety Meets Corporate Compliance, written by James A. Koph, F. Lisa Muriba, Esq., and Rory Jaffe, MD, MBA. To purchase a copy of the book, go to www.hcmarketplace.com or call customer service at 800/650-6787.
The American Medical Association looks to ensure access to all trial data, both positive and negative

The American Medical Association (AMA) is receiving support in its quest to encourage the government to establish a national clinical trials registry to improve reporting of research results, according to a written release posted on the organization’s Web site.

Several members of Congress have said they might be willing to introduce the legislation that would make the database a reality. Other organizations, including pharmaceutical companies, have signaled their support as well (see related box at right).

The AMA announced in June plans to urge the federal government to create a new registry of clinical trials. “The new registry would ensure that trials with negative and positive results are publicly available, by providing every clinical trial with a unique identification and ensuring publication or placement on an electronic database of all results from registered trials,” states a press release issued by the AMA.

The database would assign each trial a unique identification and register it in the database. The AMA also recommended that IRBs ensure registration by making it a condition for protocol approval.

The recommendation was made in response to concerns about publication bias created by commercial support for drug trials.

“Studies with positive findings are more likely to be published than studies with negative or null results,” said AMA Trustee Joseph M. Heyman, MD, in the release. “We’re concerned that this pattern of publication distorts the medical literature, affecting the validity and findings of systematic reviews, the decisions of funding agencies and, ultimately, the best practice of medicine.”

The AMA determined that clinical trial agreements between investigators and sponsors might delay the publication of results or delete certain information. Outcome bias also exists, according to the AMA. Too often, unreliable methods, inadequate sample size, or insufficient comparison groups are used during trials, which bias the results, according to the release. “Industry-funded studies may be more likely to use placebos or inactive controls, increasing the likelihood of achieving positive study results,” states the release. The AMA also determined that medical journals are more likely to publish trial results that will change clinical practice, and therefore, many negative trial results are not printed.

Organizations that back more complete reporting of trial results

The American Medical Association has received backing from several organizations for its clinical trials registry. Other organizations have said that they too support more complete reporting of trial results. Among them are the following:

- **Merck & Co.**—The drug maker supports expanding an existing clinical trials registry to include all drugs.
- **International Committee of Medical Journal Editors**—This organization is mulling over a proposal to require trials to be registered before their results are published.
- **Pharmaceutical Research and Manufacturers (PhRMA)**—The executive committee of the PhRMA has adopted a set of principals that call on drug companies to commit to reporting positive or negative trial results in an “objective, accurate, balanced and complete” manner, according to a statement posted on the organization’s Web site.
- **GlaxoSmithKline**—Europe’s largest pharmaceutical company has announced that it will publish clinical trial results for marketed drugs in an online database in the wake of a lawsuit filed by New York Attorney General Eliot Spitzer. In June, Spitzer filed suit against the company, alleging that it withheld trial data showing that Paxil increased the risk of suicide in children and adolescents and was often ineffective in treating that population, according to Reuters.
Enforcement watch: Actions taken for noncompliance

Editor’s note: Each month, CTC will look at enforcement actions taken by various federal agencies for noncompliance. We’ll update you on the most recent FDA warning letters, OHRP determination letters, FDA debarments, and actions taken by the Office of Research Integrity to restrict or debar investigators.

FDA warning letters

The FDA inspected the clinical site of Peter A. Englehard, DO, president of Apex International Health in Miami Beach, Florida, between February 5–10. The inspector found that the investigator was using unapproved informed-consent forms that did not contain all of the required elements, including failure to indicate description of the study. Additionally, the inspection found the following:

- No evidence that Englehard selected monitors or qualified them for the study
- Insufficient or lack of follow-up with subjects and failure to conduct a laboratory blood test after the required six months
- Several subjects were injected with more than the maximum allowable amount of study drug
- Failure to maintain complete, accurate, and current records, including information of discrepancies between recorded and actual inventory of devices, and subject’s case history and exposure to the device
- The site violated Investigational Device Exemptions and Protection of Human Subjects codes

The FDA inspected the Institutional Review Committee at Downey Regional Medical Center in Downey, CA between January 20–23. The FDA letter to Pramod Multani, MD, IRB chairman, informed him of violating the IRB and IRB review and approval codes. Specifically, the inspection revealed the following:

- Insufficient written IRB procedures. (e.g., detail regarding how review of research is conducted)
- Failure to meet membership requirements (e.g., having at least one nonscientist member and having a member unaffiliated with the institution since July 2000)
- Incomplete records of IRC’s members, rendering the FDA unable to determine whether membership requirements were met
- Deficiencies cited during previous FDA investigations had not been corrected

OHRP to require IRB registration

In July, the OHRP proposed a registration mandate for all IRBs that review human subjects research that is “conducted or supported” by the Department of Health and Human Services and that are designated under an assurance of compliance approved for federal wide use, according to a press release issued by the OHRP.

“The proposed registration requirements will make it easier for OHRP to convey information to IRBs and will support the current IRB registration system operated by OHRP,” states the release.

The FDA was also expected to publish a proposed rule regarding FDA IRB registration requirements, according to the release.

Currently, the OHRP requires some IRB submissions, but others are voluntary. The comment period on the OHRP notice closes on October 4. For more information go to www.hhs.gov/ohrp/news/irbnotice.pdf.
Ask the expert: FDA requirements for clinical trial standard operating procedures

This month’s experts are Mark Mathieu of PAREXEL International Corporation and Douglas Mackintosh, DrPH, MBA, MS Hyg, and Vernette Molloy, MBA, RN, both of GCPA, Inc.

What are the FDA’s requirements for and expectations regarding standard operating procedures (SOP) for clinical monitors, clinical trial sites, and others involved in clinical trials?

Interestingly, the FDA’s drug regulations include SOP requirements only for IRBs. 21 CFR 56.108 requires IRBs “to follow written procedures” and 21 CFR 56.115(a)(b) requires that these written procedures be retained.

FDA regulations include no specific references to, or requirements for, SOPs for sponsors or clinical investigators. For clinical investigators, there are no references to SOPs in FDA regulations, FDA site inspectional guidances, or the International Committee on Harmonization Good Clinical Practices guidance.

However, FDA compliance-related documents establish a clear agency expectation that sponsors will maintain and follow documented SOPs. And, as an agency official recently noted in informal correspondence regarding sponsor SOPs, “FDA, of course, expects SOPs to be followed.”

Perhaps the clearest references to the FDA’s expectations regarding SOPs for drug sponsors appear in the agency’s Compliance Program Guidance (CPG) Manual, Program 7348.810, which provides instructions to FDA field inspectors on conducting compliance inspections of sponsors/monitors and clinical research organizations. Specifically, the document makes references to sponsor SOPs in several areas, including monitoring procedures, activities and data collection and handling procedures, quality assurance auditing/quality assurance unit operations, and electronic trials.

Although CPG 7348.810 makes reference to a sponsor’s SOPs for monitoring procedures and activities, it also allows for the circumstance in which there are no SOPs. In its instructions to FDA field inspectors, CPG 7348.810 states the following:

- “Review the procedures, frequency, scope, and process the sponsor uses to monitor the progress of the clinical investigations. (Device regulations [21 CFR 812.25(e)] require written monitoring procedures as part of the investigational plan.)”

- “Obtain a copy of the sponsor’s written procedures (e.g., SOPs and guidelines) for monitoring and determine whether the procedures were followed for the selected study. In the absence of written procedures, conduct interviews of the monitors as feasible and determine how monitoring was conducted.”

- “Obtain a copy of any written procedures [SOPs and guidelines] for data verification” (i.e., the monitor’s review of subject records).

Although it is assumed that sponsors will be cited if they do not follow SOPs in these areas, it is interesting to note that CGP 7348.810 specifically instructs agency investigators to document deviations only regarding SOPs for data collection and handling procedures as follows:

1. Review the sponsor’s written procedures (i.e., SOPs and guidelines) to ensure the integrity of safety and efficacy data collected from clinical investigators (i.e., domestic and international).

2. Verify that the procedures were
followed and document any deviations.

**Q. What does the ICH GCP guidance say about SOPs?**

A. As noted, the ICH GCP guidance does not make mention of investigator SOPs. The guidance, however, makes several references to sponsor SOPs, which it defines as “detailed, written instructions to achieve uniformity of the performance of a specific function.” Specifically, the ICH GCP guidance states the following:

- “The sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written SOPs to ensure that trials are conducted and data are generated, documented [recorded], and reported in compliance with the protocol, GCP, and the applicable regulatory requirement(s).”
- The sponsor should maintain SOPs for using electronic trial data handling/remote electronic trial data systems.
- Monitors should follow and be thoroughly familiar with the sponsor’s “established written” SOPs and should communicate SOP deviations to the investigator.
- The purpose of a sponsor’s internal audit of a trial, which is separate from routine monitoring or quality control functions, “should be to evaluate trial conduct and compliance with the protocol, SOPs, GCP, and the applicable regulatory requirements.
- “Noncompliance with the protocol, SOPs, GCP/applicable regulatory requirement(s) by an investigator/institution, or by member(s) of the sponsor’s staff should lead to prompt action by the sponsor to secure compliance.”

Editor’s note: These questions were excerpted from nearly 400 Q&As in the second edition of Good Clinical Practices: A Question and Answer Reference Guide (May 2004). Go to www.barnettinternational.com for more information on the publication. Reprinted with permission.