Journal of Investigative Medicine 56(8):975–984, 2008

Clinical Research From Proposal to Implementation: What Every Clinical Investigator Should Know About the Institutional Review Board

Suzanne M. Rivera, PhD

■ ABSTRACT

The conduct of clinical trials is a complicated process involving a myriad of regulations and enforcement entities. To protect the rights and welfare of study participants, a system of oversight bodies called institutional review boards has been established in the US. This article describes how institutional review boards work and explains what clinical researchers need to know about federally mandated human subject protection requirements.

Key Words: institutional review board, research proposal, research implementation, IRB

The conduct of clinical trials is a complicated process. Researchers and study sponsors are required to comply with a myriad of regulations enforced by numerous oversight entities. The federal Policy for the Protection of Human Subjects issued (45CFR§46) by the Department of Health and Human Services (DHHS) governs biomedical, social, and behavioral research. These regulations, first promulgated in 1981, have become the US national standard for the conduct of human research. Having now been adopted by 16 other federal agencies, the policy usually is referred to as *The Common Rule*. All institutions (domestic and international) that accept US federal dollars for human research must assure, via a binding agreement with the DHHS, that they will comply with the common rule.

The common rule requires that research involving human subjects must be reviewed by a committee called an institutional review board (IRB). According to the federal definition, human research "means a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge and which uses living humans or identifiable information about living humans."[1] This definition includes everything from randomized clinical trials to questionnaires. At universities and hospitals, virtually all research done with people, or with private information about people, is subject to IRB review.

From the UT Southwestern Medical Center, Dallas, TX.
Reprints: Suzanne M. Rivera, PhD, UT Southwestern Medical Center, Dallas, TX. E-mail: suzanne.rivera@utsouthwestern.edu.

■ WHAT IS AN IRB?

Institutional review boards are committees that review and oversee human research studies. At universities and hospitals, IRBs are comprised mostly of physician researchers, nonphysician scientists, and administrative personnel, such as attorneys and risk managers. Frequently, allied health professionals, such as nurses and social workers, also participate. In addition, federal regulations require that each IRB must have at least 1 unaffiliated member ("community member") who can represent community perspectives. Often this is a layperson, such as a member of the clergy.

The federal government designed IRBs to be local committees specifically so that they would represent local community interests and standards. This means that a study approved in Dallas might not receive approval in Boston or Seattle. The idea of local review and oversight is that knowledge of local patient populations, local resources, and the skills and experience of local researchers are to be taken into account when the IRB reviews a protocol.

■ WHAT DOES THE IRB DO?

The top priority of an IRB is human subject protection. Sometimes this can seem at odds with investigator priorities, which also may include curing disease, adding publications to a curriculum vitae, or supplementing a salary to please a department chair. Institutional review board members (most of whom are faculty researchers themselves) generally think those things are important, too. But their primary focus during IRB review is the protection of human subjects.

Toward that end, IRBs are charged with upholding and enforcing *all* applicable human subject protection

requirements: federal, state, and local. As noted previously, the DHHS regulations known as the common rule are the primary regulations for protection of human subjects. In addition, the U.S. Food and Drug Administration regulations at 21 CFR Part 56 govern drug and device experimentation and regulations promulgated by the DHHS office of civil rights protect subject privacy (Health Insurance Portability and Accountability Act, HIPAA). In addition, each state has it own research-related statutes, and all universities and hospitals have research policies and procedures. Institutional review boards must know and adhere to all of these. Ideally, IRBs help investigators understand and comply with these requirements as well.

■ WHAT DOES THE IRB NEED TO REVIEW?: FOUR KEY POINTS

When deciding whether an activity requires IRB review, it is helpful to parse the federal definition of human research.

1. Is the activity systematic? A case report of 1 patient who had an unusual drug reaction can be written up, submitted to a journal, and published, but it is not a "systematic investigation…designed to develop or contribute to generalizeable knowledge."[1] By contrast, the deliberate review of multiple case reports in order to generalize the results would constitute a systematic investigation.
2. What is the intent of the investigation? To be considered research, an activity has to be designed in order to develop or contribute to generalizable knowledge. A systematic investigation that involves humans for a purpose other than generating scholarship does not require IRB review. For example, if someone were to undertake a systematic survey asking every third visitor to an office whether the receptionist smiled at them, and if the reason for doing so is to give the receptionist feedback in an annual performance evaluation, then IRB review is not required. However, if the purpose is to write up a paper for a human resources journal about the general level of satisfaction with receptionist friendliness in university administration offices, such a project would need IRB review. For IRB review to be required, it is not necessary to actually make a scholarly contribution but merely to have scholarly intent. Even if an experiment fails or a manuscript never gets published, the time to ask for IRB review is before starting an experiment if the intention is a research purpose.
3. Are the people under study alive? The federal definition of research covers living humans—not decedents. However, if your research requires collecting data about living humans who are related to the decedents under study, or if you are doing a genetic study that gives you information about the decedents' offspring and such data will be used in the research, the project becomes human research subject by the federal definition. Be careful about knowing your state law on this issue. Most states do not treat research on decedents as human research. However, some states, such as California, recently have passed laws making research on decedent data and use of cadaveric tissue human research for purposes of IRB oversight.
4. Is the information identifiable? By identifiable, we mean whether the research team has access to identifiers at the time of data collection. For example, a retrospective review of medical charts is human research, even if the researcher does not collect the identifiers for purposes of the study. On the other hand, data that already have been aggregated or de-identified, meaning no individual respondent-level information is available to the researchers (although the information is about living humans), does not meet the federal definition of human subjects research.

In summary, if your investigation is systematic, is done with scholarly intent, and uses humans or identifiable information about living humans, your project meets the federal definition of human subjects research and requires some degree of IRB oversight.

■ LEVELS OF IRB REVIEW

There are different levels of IRB review depending on the degree of risk posed by a given research study. Investigators need to decide what category of review is appropriate in order to prepare the IRB application. Depending on the research design and the population to be studied, a protocol may qualify for "exemption" from IRB review, for an "expedited" IRB review (which means IRB review by a subcommittee), or for a full-board (ie, convened meeting) IRB review. Institutional review boards usually have knowledgeable staff that can help investigators to make that determination.

Exempt

"Exempt" means that actual IRB approval is not federally required; however, most institutions require a written validation of exempt status. Usually, verification of exemption is a very simple process. There are 6 categories of exempt human research defined by regulation, all of which involve virtually no risk to subjects. Examples include retrospective chart reviews when identifiers will not be collected by the researchers, studies of existing de-identified medical specimens, surveys and questionnaires on nonsensitive topics, and taste tests. Verbal consent is appropriate for most kinds of exempt studies, and in many cases, a waiver of consent may be granted.

Expedited

The next level of review is called "expedited." Although this term makes it sound like the review happens extra quickly, in this context, "expedited" simply means the review is performed by a subcommittee of the IRB, rather than by the full board at a convened meeting. According to regulation, to qualify for the expedited subcommittee review, these studies can pose "no more than minimal risk"[1] to subjects, which means no more than the risks of everyday life or a routine medical or psychological examination. For example, a routine medical examination might include measurement of height, weight, blood pressure, some blood work, and urinalysis, but not inoculation with an experimental vaccine. Like the exempt level, there are federally-defined categories for expedited review. Written consent often is required, but can be waived by the IRB. Investigators frequently are given permission to obtain verbal consent for expedited studies because they pose no more than minimal risk. The IRB must perform a continuing review of expedited studies at least annually.

Full Board Review

If a study does not qualify for exemption or expedited review, it must be reviewed at a convened meeting of the full board. These studies involve more than minimal risk to subjects, meaning the risks are higher than those we normally encounter in our everyday lives or at routine medical or psychological examinations. Written consent is required for almost all full-board studies, although there are provisions for waiving consent in some circumstances. Again, continuing review is required at least annually. If an IRB has specific concerns about the safety of a particular study, it can mandate continuing reviews more frequently, such as every 6 months, each quarter, or after a certain number of subjects is enrolled.

■ APPLYING FOR IRB REVIEW

Submitting a protocol to the IRB for review requires familiarity with local IRB procedures. At most institutions, the IRB will have a Web site with application forms and instructions for completing them. Customarily, there is an application form or cover sheet that must be completed by the principal investigator (PI) to initiate the review. That form usually is accompanied by a concise summary of the project (some IRBs call this the "protocol narrative"), an informed consent document (unless requesting a waiver of informed consent), a HIPAA waiver and/or authorization (if needed), and the master protocol and investigator's brochure (these are provided by the pharmaceutical company if it is a clinical trial performed under a contract with a sponsor). If the study is investigator-initiated, there usually will not be a master protocol.

When preparing an IRB application, it can be helpful to use a submission checklist. For example:

1. Make sure that all study personnel have been trained on human subject protection requirements in accordance with local IRB policy. Often the required training is available online. Consult your local IRB to find out if collaborators outside your institution need to take your local IRB training in order to be listed on a protocol application.
2. Be certain that all the required components are included in the submission packet. Protocol reviews frequently are delayed simply because the packet is missing an essential document, such as an informed consent form or a master protocol.
3. Provide enough information to the IRB so that they can make a decision. This is especially true when proposing a study that is controversial or ethically provocative. If the study is likely to raise IRB "eyebrows," be proactive about providing a rationale in terms the IRB members can understand. For example, when reviewing a placebo-controlled trial of a new drug to treat a disorder for which there is a safe and efficacious treatment already on the market, the IRB will want to know that thought has been given to whether it is ethical to deny treatment to the control arm for the duration of the study, and why the benefit of this study outweighs the risk to those individuals who go untreated during the trial. Similarly, if a study is designed to obtain informed consent from women who are in active labor, the IRB will want an explanation of why the research cannot be done in some other population that is not in pain and under duress. If it appears to the IRB members that there is not a well thought-out reason for conducting an ethically provocative study, they are likely to defer the application pending further dialogue with the investigator.
4. Avoid unnecessary jargon and abbreviations. This is important not only because it is hard for the scientific members to review a protocol in another scientific discipline, but–more importantly–it is critical for the unaffiliated "community members" sitting on these boards. If you give a highly technical explanation of the proposed study, laypeople sitting on the IRB simply may not be able to understand it. Keeping the protocol documents relatively free of jargon greatly facilitates the review process.
5. Double-check grammar, syntax, spelling, and formatting. Ask a colleague to proofread the drafts. Scientists frequently criticize the IRB for nitpicking spelling but IRB members often have 2 kinds of legitimate concerns when sloppy documents are submitted for review. First, when asking the IRB to authorize an experiment on humans, it should be evident that sufficient thought

and attention has gone into the study proposal. When an investigator cannot be bothered even to run a spell-checker, it suggests s/he is not giving the project adequate attention. Second, it is important to note that occasionally typographical errors really matter. The difference between "by month" and "by mouth" in an informed consent document is both substantive and important to subject safety.

■ THE IRB REVIEW

Once a protocol application comes to the IRB for review, a number of considerations are made by the members.

First, the panel will consider whether the study design is consistent with sound research principles and ethical norms. Although IRBs are not expected to assess scientific merit like study sections, they are charged with assuring a favorable risk-to-benefit ratio. If a scientific design appears so fundamentally flawed that meaningful results will not be possible, the IRB will not be able to justify authorizing even the most modest risks or inconveniences to subjects. The burden is on the PI to explain his/her proposed study design in a way that will show it is possible to answer an important scientific question.

Next, the IRB will determine whether the potential benefits are maximized and the anticipated risks are minimized. In other words, if the study involves a known risk, are there plans to monitor, limit, reverse, or otherwise mitigate it? For example, if a study involves administration of a drug that causes dizziness, will subjects be given a place to lie down or taxi vouchers so they do not try to drive themselves home?

Similarly, if a study benefit can be maximized, there should be plans to do so. A common way to maximize benefits for study subjects is to share with them information relevant to their medical care. If the study involves testing for disease prevalence in a population, the IRB may ask whether plans have been made to refer subjects for treatment in the event of a clinically-relevant finding.

Another important consideration made by the IRB is whether the plan for selection of study subjects appears equitable. One of the pillars of human subject protection is the principle of justice. This means that we ought not burden vulnerable populations unduly nor reserve the benefits of research only for the very privileged. Institutional review board members will review the recruitment plan and will raise questions about who may be targeted specifically or left out (whether intentionally or by default).

Institutional review boards also must evaluate whether all the necessary elements of informed consent have been included in the consent form that will be given to subjects. The required consent elements are listed in *The Common Rule* and most research institutions host a link to them on the Web site of the local IRB. Some IRBs also have an informed consent template that researchers can use to help prevent leaving out a required element while drafting the consent document.

Protection of subject privacy is another important issue considered by the IRB. The study plan will be scrutinized to assure that all necessary precautions are in place to protect subject privacy and to preserve confidentiality of study data. In this age of rapidly-changing technology, procedures for data collection and storage have become highly complex. It is important to explain not only where hard copies of paper consent forms will be kept under lock and key, but also what schemes will be used for encryption of digital data, firewall protection of computers, and even how hackers will be prevented for intercepting data collection and transmission using web-portals, handheld (mobile) devices, or remote sensors.

Finally, IRBs are mandated to consider whether additional safeguards are in place to protect especially vulnerable subject populations. For example, if children will be studied, there must be a plan for obtaining parental permission. It also may be appropriate to seek assent from the minor subjects. Similarly, the study of decisionally impaired people usually requires plans to obtain consent from the subjects' legally authorized representatives. Other categories of special populations requiring extra protections include prisoners, pregnant women and fetuses, and subordinate employees of the researcher.

■ OF SPECIAL CONCERN TO IRBS

Beyond the extra protections required for vulnerable subject populations, IRBs frequently are concerned about other special topics related to human subject protection.

Show Me the Money. Research risks are not only physical; they also can be emotional, and even financial. If a researcher proposes to bill subjects for the experimental drug or device under study, the IRB members will want to know why. Is there a reason that the company sponsoring the trial is not providing their product free to subjects? Sometimes billing subjects or insurers for study-related expenses can be appropriate, such as in cancer cooperative group trials comparing 2 accepted standards of care, but it is important to provide a justification.

Exclusion of Non-English Speakers. Regulations require that informed consent is documented in a language understandable to the subject. Unless written consent is waived, that means getting it translated in writing into the language(s) that the likely subjects speak. This concern relates to the question of whether the distribution of risks and benefits in society is equitable. An IRB will not likely be sympathetic to a statement like, "Non-English speakers will be excluded because we do not want to

spend money to translate the consent form." However, there can be legitimate scientific reasons for language exclusions. For example, "We must exclude non-English speakers from this psychiatric study because the data collection instruments have not been validated in any language other than English."

Off-Site Research. Researchers proposing to conduct experiments outside their institution of employment should expect to provide extra documentation. Frequently, an IRB will require evidence that the proposed off-site study locations have given permission to conduct research on their premises. If the off-site institution(s) has an IRB, chances are that their IRB also will want to review the study before the work begins at that site. Consultation with your local IRB about requirements for authorization of off-site research can save a lot of time.

Drugs, Devices, and Biologics. The FDA regulates experiments using new drugs, devices, and biologics by issuing permission to use Investigational New Drugs and through Investigational Device Exemptions. Frequently, investigators want to test an existing drug for a new indication. That also sometimes needs an Investigational New Drug, so it is important to consult with your local IRB whenever planning a study that involves the use of drugs. When a clinical trial is sponsored by industry (whether a pharmaceutical company or a device manufacturer), chances are they already obtained FDA permission for the trial before recruiting investigators. This is something the PI should verify before applying for IRB approval locally.

Health Insurance Portability and Accountability Act. This relatively new law affects research involving the creation, use, or sharing of identifiable health information. At many academic medical centers and hospitals, the IRB acts as the "privacy committee" required by HIPAA, meaning that it reviews the plans for protecting private information about patients. Depending on the study design, you may need to provide a HIPAA authorization and/or a HIPAA waiver request to your IRB with the application to conduct human research. The HIPAA waiver is a document that allows a researcher to access people's private information without their knowledge or permission. For example, if a PI wants to review 500 medical charts of people with a certain diagnosis, she/he would need permission from the IRB to conduct the study and also would need a HIPAA waiver to look at the charts without getting permission from the patients themselves. A HIPAA authorization is different. A HIPAA authorization is something that a PI will use to get permission from the study subjects to access their private health information or to transmit their private information to another entity. For clinical trials, subjects typically sign both the research informed consent form and a HIPAA authorization permitting use of their health information for the study. At some institutions, the HIPAA authorization language is integrated into the research informed consent document; however, some states have laws that prohibit this.

Certificates of Confidentiality. When a study involves collection of information that is potentially stigmatizing (eg, could put someone at risk for legal prosecution, being fired, getting deported, or put on the news and shunned by their friends and neighbors), the IRB may ask an investigator to apply for a certificate of confidentiality from the National Institutes of Health (NIH). This document protects an investigator from having to disclose any research-related information to a requestor, even under a subpoena. For example, if a subject is in the middle of divorce proceedings, and the PI of the study gets a subpoena from the husband's attorney requesting study records to see if the wife disclosed drug use on a study questionnaire, a certificate of confidentiality would allow the PI to respond, "I'm sorry. I can't even confirm that person was in this study. I have a certificate of confidentiality from NIH."

Genetic Testing. Protocols involving the use of genetic tests get extra scrutiny from IRBs for several reasons. One major concern is the possibility that the information derived can place subjects at risk for discrimination by employers and health or life insurance companies (accordingly, the IRB may recommend a certificate of confidentiality). Another issue is the psychological distress that may be experienced by subjects who learn of a genetic predisposition to develop a disease. In addition, genetic studies sometimes can yield unexpected findings, such as misattributed paternity. For these and other reasons, many IRBs require additional consent language to inform subjects about the particular risks associated with genetic testing. Some IRBs even require the use of separate genetic research consent forms or consent form appendices to address these concerns in greater detail.

■ COMMON REASONS FOR IRB DELAYS

Institutional review board approval can be delayed for any number of reasons. Keep in mind that the IRB staff members whose job it is to write those IRB determination memos are just the messengers. The voting members who sit on the boards–your colleagues–make the decisions. Although it might feel really good to yell at the IRB staff when you do not like an IRB decision, it does not actually result in your protocol getting approved any faster.

To help you avoid common pitfalls, here is a list of the top 10 reasons for IRB delays.

1. Research team members have not completed required human subjects protection training.
2. Required signatures or authorizations are missing. Most IRBs require a signature (electronic or hard copy) from the lead researcher and some sort of permission or concurrence from his/her department chair or supervisor.
3. Research is to be conducted off-site and evidence of permission from the off-site institution is not provided.
4. Protocol requires review by another institutional entity. At most institutions, the IRB is one of many review bodies that must authorize a study before it can begin. For example, if the protocol is cancer-related (which includes cancer prevention, cancer treatment, cancer survival or even quality of life for cancer survivors), review by the protocol review and monitoring committee of the cancer center usually is required before the study can be approved by the IRB. Similarly, if the study involves radiation (eg, x-rays, positron emission tomography scans), approval from the radiation use committee may be required.
5. Significant discrepancies between the protocol and consent form. Institutional review board members review the documents submitted by the PI carefully.If the protocol says there is a risk of hair loss, dizziness, and occasionally death but the consent form lists only the risk of occasional hair loss, the IRB will ask the investigator for revisions to ensure consistency.
6. Recruitment procedures and informed consent process not adequately explained. It is not enough to simply request 100 subjects. The methods of recruitment and sources of subjects are important, too. Tell the IRB if you plan to recruit from among your own patients or from an on-line chat room for potential participants. The "how" is as important as the "who."
7. Anticipated risks to the participants not justified. Although it is perfectly acceptable to propose procedures that are risky for subjects, there must be corresponding benefits for subjects and/or for society. A rationale for the known risks must be provided in the protocol.
8. Inadequate safeguards to protect data from a breach of confidentiality. If the safeguards are not sufficient, the IRB will ask for more information to assure that risks associated with unauthorized access to subjects' data are minimized to the fullest extent possible.
9. Consent form deficient. If the consent form is missing required elements, or if the reading level is too high or contains too much jargon, the IRB will ask for revisions.
10. No scientific justification for exclusion of non-English speakers or no description of plan to enroll non-English speakers. In some parts of the country, this is not a frequent IRB concern. However, in most urban areas and in all of the southwest, IRBs pay great attention to language issues both because of the potential for inadvertent exclusion of otherwise eligible subjects and because of the requirement that consent be understandable to subjects.

Study Management

Once you have IRB approval, regulations and requirements that affect the conduct of the study must be followed. From the perspective of the IRB, these are the most important things to keep in mind.

Recruitment. One thing that often is not understood is that recruitment is the beginning of the informed consent process. For this reason, the IRB must approve the text of any poster, classified ad, radio spot, e-mail message, or television commercial used to recruit study subjects.

If you place an advertisement in the newspaper or put flyers up around a campus to interest people in your study, it is really important that the ads are not misleading. This is especially of concern when recruiting for clinical trials of drugs and devices because the FDA has specific requirements for what can (and cannot) be said in a study recruitment ad.

Overemphasizing financial inducements may cause potential subjects to consider the reward first and the potential risks later. For this reason, an ad that says, "FREE HEALTH CARE! FREE DRUGS! EARN $500 TODAY!" in all capital letters, bolded, and underlined will be perceived by the IRB as undue pressure and would not likely be approved.

Keep in mind that the methods of advertising proposed in the recruitment section of your protocol narrative are the ones the IRB expects you to use. If you find that the recruitment strategy that you originally proposed is not working and you are not able to accrue subjects as quickly as you wanted, then you need to submit a modification request to the IRB saying that you would like to change methods for recruitment and describing the proposed changes.

Enrollment. Consent is a process, not a document. Although the IRB scrutinizes the informed consent form to make sure it contains all the required elements, the paper form is meant to memorialize the fact that a dialogue took place between researcher and subject about the risks and benefits of participation. Signing the form is a formality that should follow a verbal invitation, a thorough explanation of the facts, and an opportunity for the subject to ask questions and consider without pressure whether or not to enroll.

Keep in mind that once the informed consent form is approved by the IRB, the approved form is the only version you should use to document the willingness of a subject to participate in the research project. Some investigators will photocopy the original version approved by the IRB. Others will scan it and host it on a shared drive so that other people on the study team can download it and print it off. Either way is acceptable, but it is essential to use the approved version. Do not alter or add to an IRB-approved informed consent form.

Modifications. Any change to an approved study must be approved by the IRB before you make that change. This includes adding a new member to the study team, changing study procedures, changing subject populations, and adding recruitment methods. Most IRBs have a form for requesting permission to modify a study. In rare circumstances, a PI may alter a study procedure to avoid an immediate apparent hazard to a subject without prior IRB permission; however, these deviations should be reported to the IRB as soon as possible.

There are 2 kinds of IRB modifications. A minor change can be reviewed via the expedited method (ie, by subcommittee). Any significant change (one that affects the risk-benefit ratio or substantially changes what the study is trying to accomplish) must be reviewed by the full board at a convened meeting. Sometimes an IRB will determine that significant changes resulting in new informed consent language warrant "re-consenting" of already enrolled subjects because the new information may affect their willingness to continue participating.

It is the significance of the modification itself that affects whether it goes to full board or is expedited, not the initial level of review of the study. Therefore, a significant change to an expedited study could still go to the full board. Likewise, a minor change to a full board study can be reviewed via the expedited procedure. Frequently, significant changes to expedited studies cause them to become full-board studies.

Adverse Events and Unanticipated Problems. Any time something happens to a subject that is not good and that was unexpected (ie, not identified as a known risk in the informed consent document), the incident must be reported to the IRB. Many IRBs have an "Adverse Event" (AE) form for this purpose. The most serious AEs (called SAEs), which are death, hospitalization, prolongation of a planned hospitalization, and birth defects, need to be reported to the IRB immediately–preferably by phone or fax–and followed by a written report.

Even events that do not appear to be related to the study intervention are reportable. Some investigators may assume, for example, that a broken arm need not be reported because it does not appear to be a study-related injury. However, seemingly unrelated events can signal new, previously unknown risks. If 5 subjects on a trial break limbs in a 1-month period, it may suggest that the study drug causes dizziness. Only if these events are reported can the IRB do the type of trend analyses that can identify new risk information. Such information is vital, not only because it informs the IRB's decision about permitting the study to continue, but also because it is essential for keeping the informed consent document complete and up-to-date.

The IRB takes into account the health of the subjects when it reviews AE reports. Studies including sick populations will be expected to report multiple hospitalizations and even deaths. However, a study of healthy volunteers with lots of unanticipated hospitalizations will raise red flags.

It should be noted that the IRB is not a Data Safety and Monitoring Board (DSMB), and it may have difficulty interpreting AE data for a multisite study sponsored by a pharmaceutical company. Local IRBs only have complete information about subjects enrolled onsite, so they must rely on the sponsor monitors and the national (or international) DSMB to provide a more rigorous review, inclusive of study-wide data. Institutional review boards expect that a local PI will provide DSMB reports as they are forwarded by the study sponsor or at least at the time of continuing review. These reports complement the AE reports already received in the IRB office by providing a context based on study-wide analyses.

Deviations and Violations. These 2 words often are used interchangeably to describe a variance from approved study procedures or timelines. An examination of 10 IRB Web sites at 10 universities across the country will reveal 20 different definitions of the words "deviation" and "violation." Some IRBs only use 1 word, some use only the other word, and some use both words and distinguish between them. The bottom line is that altering the approved protocol without prior IRB approval of a modification should be unusual and must be justified and documented.

For example, if a study subject is supposed to have laboratory tests on day 14 but unexpectedly has to leave town to attend a funeral and makes arrangements to have the tests performed on day 22, this is a variance from the protocol. An investigator may consider this such as a minor difference as to be irrelevant. However, a study sponsor may disqualify the subject and disregard their data. The IRB may consider an alteration to the study schedule non-compliance with the protocol. For this reason, it is important to communicate with the sponsor and the IRB when a protocol deviation or violation occurs.

Many times the sponsor will want to "pre-authorize" a deviation and may give you permission over the phone

or by fax for a variance from their protocol. Investigators should understand that approval of a study deviation by a trial sponsor does not take the place of IRB approval of a change in your protocol. Such events need to be reported to the IRB. In fact, when a study sponsor approves a deviation, they usually want to see proof that the variance is acceptable to the IRB. Most investigators find that if they forward the sponsor's authorization for a 1-time variance to the IRB, obtaining documentation of IRB acknowledgement can be relatively straightforward. An IRB chair may ask the investigator whether a modification of the protocol is warranted, and the investigator should be prepared to explain whether the circumstances at hand are likely to happen again with sufficient frequency as to suggest a modification is appropriate.

Communicating With Sponsors. Investigators should be aware that when they agree to conduct a clinical trial paid for by a private company, that company will have its own idiosyncratic procedures and its own bureaucratic jargon. Sometimes the sponsor will host a meeting to kick off a study, often in a really nice place. At this meeting, the sponsor will explain its expectations, including preferences about how they want investigators to communicate with them. It is really important to foster a good relationship with the sponsor. Decide early in the study who on your team is the designated point of contact with the sponsor and channel all communications through him/her. It is best to keep a notebook of all communications with the trial sponsor. When communicating with the sponsor by phone, document who was on the call, what was said, and when the call took place. E-mail can be handy because it is already date-stamped and it shows who sent and received the message. Print e-mails out and file them in the study notebook. The purpose of documentation is to avoid a scenario in which the sponsor authorizes a deviation by phone and you have no evidence to prove it to the IRB or the FDA.

Retain all study-related records and be prepared to show source documents. The sponsor may want to come on site periodically and look at your recordkeeping to compare your case report forms to the source documents. It can be very helpful to perform self-assessment audits periodically to make sure, for example, that the laboratory values in the patient chart match what you have recorded on the case report form.

Anything the sponsor tells you about how well (or not well) you are meeting regulatory obligations is something you should share with the IRB. If the sponsor does an on-site audit and issues a report, even if it is a clean bill of health, the documents relating to the visit should be forwarded to the IRB. In like fashion, a report that documents that, "In three cases, the PI failed to sign the consent document and did not attach a HIPAA authorization," also should be sent to the IRB.

Continuing Review. When the IRB approves a protocol, they give permission to conduct the trial for an interval of time. Usually a trial is approved for 365 days from the review date. Keep in mind that the review date may not be the same as the approval date. For example, if your protocol is reviewed in November, but you do not respond to the IRB stipulations until January, the approval date will be in January, although the anniversary of the review will be in November. The protocol approval expires the day before the year anniversary of the review date, not the approval date. Using the example previously mentioned, if your protocol is reviewed November 1 and your approval letter is dated January 14, approval will expire on October 31.

Remember that the IRB has the authority to approve a protocol for a period less than 365 days. If the committee members believe that the intervention is especially risky, if the committee is concerned that an especially vulnerable subject population is involved that needs closer oversight, or if the trial involves very sensitive issues, the IRB may approve a protocol for only 6 months. In such instances, the IRB may grant approval for enrollment of a limited number of subjects and require re-review before approving the enrollment of additional participants. Because the interval of approval is decided by the IRB and can be shorter than 1 year, it is important to pay attention to what the approval letter says.

Assuming normal circumstances, the project approval will be valid for 365 days from the date of review. Most IRBs will send a reminder memo before expiration of the protocol approval that says something like, "Your protocol approval for study XYZ is going to expire on such-and-such date, we recommend you submit your continuing review application documents ASAP." This is important because if your study approval lapses, you will be out of compliance with the federal oversight regulations. You will make your sponsor very unhappy, and–if your sponsor happens to be the federal government–they will prohibit you from spending grant funds during the period of lapsed IRB approval.

Many IRBs have a form that needs to be filled out to request a continuing review. That form captures information such as how many subjects were enrolled during the last performance period, whether there were adverse events, and whether there will be any changes in procedures or study personnel over the coming year. If the study is a multisite trial, often there will be a DSMB. If the DSMB has issued an interim report, it should be provided to the IRB at continuing review. So, get your continuing review request in before your

study approval expires, write a brief but informative progress report, locate and attach any DSMB reports that may have been forwarded to you by the sponsor. If the study is a cooperative group trial, this may come from the cooperative group coordinating board, or whoever is assigned to do data safety monitoring. Be prepared to justify either no or slow enrollment, a high dropout rate, or excessive complaints or problems.

Continuing review is not a "rubber stamp" process. The regulations require it to be a substantive review. It gives the IRB the opportunity to reevaluate the importance of the research question and the appropriateness of the risks, to analyze the adverse events, and to look at any potential need to modify the protocol or the consent. Although the IRB is not a scientific review panel, the IRB will look at the importance of the research question in the context of performing an analysis of the risks-to-benefit ratio. If a study began in 1980, and it is still ongoing in 2008, the IRB may perform a literature review on your hypothesis and find that 6 other teams around the world have definitively answered this question already. In such a case, repeating the experiment now would be of very little benefit. In such a case, the IRB may ask for a justification for exposing subjects to the research risks.

Although not usually the case, it is possible at continuing review for the IRB to require changes that are different than what the first board said at the time of initial approval. Each board consists of human beings and, by nature, human beings are idiosyncratic. The initial review board can approve a study the first time, and then at the next continuing review identify new problems. Investigators should not be surprised to receive legitimate critiques or requests for changes from year to year.

■ POSTAPPROVAL MONITORING

In addition to the routine continuing review that the IRB performs at board meetings, most IRBs also do some kind of "not-for-cause" (routine) postapproval monitoring where staff members are sent to make certain that approved protocols have been followed and all elements of a study are well documented.

Institutional review boards also conduct audits for cause in the event of a complaint, allegation, or safety concern. It might be a parent upset that his child never got paid for participation in a study. It could be an adult on a placebo-controlled trial who feels that her problem is getting worse, and she is afraid to tell the investigator because she does not want to disappoint her physician. It could be people who feel that they were unfairly screened out of a study to which they believe they deserved access.

The FDA also audits periodically. The FDA usually conducts their audits at the point when they are about to take a new drug or device to market. They want to go back and look at the data at each of the sites to make sure that the data are good before they take that next step. If the FDA comes to do an audit, the investigator should always ask to see a badge. If you do not ask to see a badge, they will write you up for noncompliance. It is not only your right to ask to see FDA identification; it is your obligation. Otherwise, you may be releasing proprietary information of the sponsor or you may be releasing subject identifying information to an unauthorized person. In such circumstances, it is important to tell your IRB if the FDA comes to conduct an audit. The IRB can assist by sitting in and answering any questions the FDA inspector may have.

Although most of the time researchers do their best to comply with all the rules, sometimes mistakes are made. When an error is inadvertent and does not appear to affect subject safety or welfare, an IRB usually will try to resolve it informally. Occasionally, IRBs encounter investigators who deliberately break a rule, willfully disregard IRB procedure, or behave unethically. Most IRBs have procedures for handling allegations of regulatory noncompliance. Often, the process begins with an administrative review. This means pulling the protocol file to see what was approved. Sometimes allegations can be dismissed right away simply by reviewing the record.

When informal resolution is not possible, the IRB does have the authority to impose corrective action. In response to concerns about noncompliance, IRBs may restrict protocol approvals to intervals shorter that one year. They can require that a PI have a "proctor" to oversee their work. The IRB also can suspend or terminate protocol approvals, which must be reported to the federal regulatory authorities, including the funding agencies (a truly undesirable outcome). In extreme cases, a PI can be told, "Doing research is a privilege, and you have just lost the privilege." This sometimes is called the "death penalty."

Beyond the restrictions that may be imposed by the IRB, universities and hospitals also can impose penalties for research noncompliance. There can be additional remedies that involve placement of letters in a personnel file, demotion, sending a retraction letter to a journal, and a number of other corrective actions.

■ CLOSING A PROTOCOL

At the end of a study, investigators should close out the protocol with their local IRB. Keep in mind that if there is a reasonable chance access to the identifiable private information will be needed again, the protocol should

remain open. However, when analyses of identifiable data are complete, it is best to close it out. For the most part, the local IRB is required to keep its records from 3 to 6 years following study closure.

■ CONCLUSIONS

In summary, the various regulatory requirements for clinical research are complicated and can be daunting. However, local IRBs usually have trained and capable personnel who can help investigators to navigate the gauntlet of forms, reports, and other obligations. In moments of frustration, it is important to keep in mind that good treatment of research subjects yields good science. Finally, the protection of human research subjects' rights and welfare is not only the right thing to do—it is the law.

■ REFERENCE

1. Code of Federal Regulations Title 45 Part 46 "Protection of Human Subjects" Revised June 23, 2005.