

# INSTITUTIONAL REVIEW BOARDS: FOUNDATIONS IN LAW

**ABSTRACT** - *This article highlights the responsibilities of Institutional Review Boards (IRBs) and the regulations and guidelines that the U.S. Food and Drug Administration (FDA) expects IRBs to adhere to in their review and oversight of clinical investigators. A foundation in law applicable to IRBs and other areas of biomedical research is provided. The way in which the law has developed into regulation, guidance, and policy will be explained. The inspection process, including current inspectional findings related to IRBs, is discussed.*

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## **The History of Research and IRBs**

The historical perspective is important in understanding some of the regulations that apply to the operation of an IRB. If you know where you came from, you have a better chance of getting where you need to go. Law can be seen as a reflection of the moral and ethical views of society. Many FDA initiatives have occurred as a result of tragic historical events.

Much of the content of the IRB regulations can be traced directly to the Nuremberg Code (1947), which provides 10 precepts for conducting human research, including the need for voluntary consent, risk/benefit analysis, avoidance of injury and unnecessary pain and suffering, qualified investigators to conduct studies, and the right of the subject to terminate participation. Between the emergence of The Nuremberg Code and The Declaration of Helsinki, first published in 1964, the Department of Health, Education, and Welfare (now called Health and Human Services) first required IRB approval for government-funded research. This came about as an outgrowth from the 1962 Kefauver-Harris Amendments to the Food, Drug & Cosmetic Act, which established the Investigational New Drug (IND) regulations. Part of these regulations called for review by IRBs. Initially, those regulations only required IRB involvement when the study subjects were institutionalized (e.g., inpatients in hospitals or

prisoners). The Declaration of Helsinki has since been incorporated as part of these IND regulations, permitting the FDA to consider reviewing studies conducted outside the U.S. if they adhere to the precepts of the Declaration of Helsinki.

In 1971, IRB review of protocols became mandatory in order for the FDA to approve an IND. However, this requirement was still limited to institutionalized subjects. In 1972, the Tuskegee Syphilis Study, which had been running since 1932, was finally stopped due to the public outcry over the patently unethical practices involved. It is sobering to note that this study had continued to run for 25 years after the Nuremberg Code was established. In 1973, the American Psychological Association passed a Code for Social and Behavioral Research, expanding the concern for ethics beyond the strictly medical realm. Then in 1974, the National Research Act was passed. This law resulted in the formation of the National Commission for the Protection of Human Subjects. In 1978, that commission produced The Belmont Report, which went above and beyond The Nuremberg Code and The Declaration of Helsinki, to codify the concepts of respect for persons, beneficence, and justice.

Also in 1978, FDA proposed regulations to govern the operations of IRBs. Prior to this, the FDA required

IRB review for IND submission, but it never said what an IRB was or how it was expected to operate. These IRB regulations were finalized in 1981, and they continue to evolve to this day. It was these regulations that finally extended IRB protection to non-institutionalized subjects.

## **Requirements of Law**

The Kefauver-Harris Amendments, which became law in 1962, called for demonstrating safety and efficacy through adequate and well-controlled clinical studies; avoiding unreasonable risk to the safety of subjects; informing subjects of investigational purposes; and obtaining consent. The law, however, is never enough. The law says what you must do, but provides little guidance on how to do it.

Regulations emanate from law, providing a framework that is built on the foundation of law. Policies and guidance statements further clarify the regulations. There are four FDA regulations relevant to IRBs: 21 CFR parts 50, 56, 312, and 812; although part 56 is most applicable to IRBs, members of IRBs need to be familiar with the relevant portions of these other regulations as well.

Guidances are suggestions that represent the agency's official view of one way to comply with a regulation. The FDA guarantees that if you follow the guidance, you will be considered in compliance with the

applicable regulation. But the guidance is neither binding on regulated entities nor on the agency. That is to say, that you are free to comply with regulations in a different way, and the FDA is free to revise guidances in writing when the need arises. The FDA's Web site ([www.fda.gov](http://www.fda.gov)) includes helpful, current information on policies and guidances, including information sheets specifically geared toward IRBs and clinical investigators ([www.fda.gov/oc/ohrt/irbs](http://www.fda.gov/oc/ohrt/irbs)).

Compliance Programs are also available on the FDA's Web site. These are valuable documents that cover inspectional procedures, reporting requirements, and inspectional follow-up options for FDA Investigators and Compliance Officers. The Compliance Program tells FDA Investigators how to conduct inspections as well as the agency's priorities. It also discusses what Investigators should include in the written report of the inspection as well as actions that the agency may or may not take once the inspection process is complete.

Although the requirements of the law itself are rather simply stated, the nuances of compliance with the law are potentially quite complicated. Table 1 captures the major points of the IRB regulations found in 21 CFR Part 56. In terms of understanding the regulations more completely, and dealing with the day-to-day problems and nuances you face, you should become familiar with some other regulations and background documents. In August 1978, the FDA first proposed the regulations for IRBs (available online in the *Federal Register*, volume 43, number 153). They became final regulations in January 1981 (*Federal Register*, volume 46, number 17). The preamble published with these final regulations provides a very good understanding of the FDA's thought process and fleshes out some background that should prove helpful when you face tough decisions. If you know how the regulators are thinking, you have a better chance of developing practices and making decisions that will protect your subjects and keep the FDA happy.

The proposed rule on the protection of human subjects (published in August 1979, *Federal Register*, volume 44, number 158) and the final rule on bringing FDA regulations into conformance with the Federal Policy for Protection of Human Subjects (*Federal Register*, volume 56, number 117) are also available online. These documents provide further explanation of how the agency thinks and why it does what it does.

#### **Problems with IRBs**

Problems found during inspections are usually due to failure of the IRB chair to: establish and maintain credibility, find the leverage point, fight for resources, and/or keep members engaged. Credibility of the IRB with the principal investigator, sponsor, institution, and FDA is invaluable. In general, you accomplish this by keeping your core mission front and center at all times. This is easier said than done in a very political environment with many competing interests.

The core mission statement, as set forth in whatever document defines the IRB and the way it operates, is probably the most important thing you can write. It should be in bold letters, perhaps red ink, and on the front cover as a reminder to everybody that this is why the IRB exists and how it intends to do its job.

Never tolerate a conflict of interest. If somebody on the IRB might have an interest in a study, you must be very careful to exclude that interest from the decision making process.

Provide meaningful reviews. The IRB should not be a rubber stamp, a spell checker, or a copy editor. The IRB must provide meaningful scientific and ethical evaluation of protocols and not be distracted by niggling little details.

Do not waste time trying to change people who will not conform to the IRB's requirements or requests. If a good faith effort does not work, turn the problem over to the person within the department or institution who has the leverage to deal with it effectively and efficiently.

IRBs require sufficient qualified members to review protocols. Freeing up the time for members to conduct meaningful review is very important and very difficult, but if an institution wants to conduct good research, the institution must commit to providing the necessary resources. The institution must make qualified people available, prod them if need be, and give them the time to do their work. This is not the job of the IRB chair; it is the function of the institution.

Most IRBs today are inundated with so much work that they are forced into doing primary review, where a protocol goes to a small number of people who have responsibility for taking a good, close look at the protocol, investigator's brochure, consent document, and everything else. If you find it necessary to operate in this way, shuffle the deck now and then and mix your primary review teams so that they have the opportunity to learn from working with different people. If you have an unusual

**TABLE 1**  
**Major Provisions of 21 CFR, Part 56**

- Review and approve or reject clinical research involving humans - Initial
- Review and approve or reject clinical research involving humans - Continuing
- Maintain proper membership numbers, qualifications, and affiliations
- Establish written procedures to follow in fulfilling requirements of the regulations
- Keep adequate records
- Communicate decisions

protocol, bring in an extra reviewer or two, hopefully with appropriate special expertise. Do continuing education when time permits and bring in consultants, when necessary, for special reviews.

### The Inspection Process

You have already been doing what you need to do day in and day out. The FDA is just coming to inspect and confirm that your day-to-day efforts stay on track. Table 2 outlines some suggested ways to prepare for an FDA inspection. As the chair or contact person, allow about 30 minutes for the initial interview. Provide some space for the inspector to work. These inspections get pretty intense in terms of documents required for review, so it is helpful to have a desk or a table where the inspector can spread out in order to audit and compare records.

**TABLE 2**  
**Preparing for an FDA IRB Inspection**

- Allow time for the initial interview
- Provide working space for the inspector
- Provide access to files and someone who knows where things are in the files
- Provide access to a copier or to someone to make requested copies
- Be reachable by phone or pager during the day
- Be available at the end of each day for wrap-up

Providing ready access to files, correspondence, and records goes a long way toward making the inspection process efficient. It is also crucial to have someone available who knows how the IRB operates and where things can be found in the files. This knowledgeable individual can be the chairperson, a coordinator, or an administrator.

Inspectors normally do a lot of copying, so having a copier nearby or someone to make copies is a major help. The chairperson should be reachable by phone or pager during the day in case something comes up that is a sticking point, i.e. something the inspector cannot get past without

consulting the IRB chair. Typically, the inspector will request a little time with the IRB chair at the end of each day for wrap-up, to explain findings, discuss next steps, and sometimes, to deal with issues and seek answers to questions.

The inspectional process begins with an assignment from headquarters and then a call from the inspector to schedule the inspection. When the inspector arrives, he/she will show official credentials and issue a Notice of Inspection. If the person does not have credentials, do not let him/her in. The inspector will ask a lot of questions, review procedures and records, and ask more questions based on this review. The Compliance Program mentioned earlier will give you a good idea of the areas of interest. He/she may or may not issue

a List of Inspectional Observations at the end of the inspection. Whether you receive this written list or not, the inspector will discuss findings with the IRB chair. Not all findings rise to the level of requiring a written observation.

The FDA is currently in the process of computerizing its List of Inspectional Observations. Whether computerized or not, the list will include a lead-in statement indicating that: "These observations do not represent final agency determination regarding your compliance. If you object to an observation, you may discuss the objection with the FDA investigator or submit it to the FDA at the address

above." In essence, this says that the investigator is not the judge, jury, and executioner; he/she is a fact finder. The investigator asks questions, gathers information, puts together a report, and submits it for review. The investigator will notify the IRB chair of perceived problems, but there is room for discussion and sometimes disagreement on these inspectional findings. Often, it is a matter of making sure that the inspector and the IRB chair are on the same page.

Many people see the FDA inspection as an onerous process, but it does not have to be that way. Part of the reason for the daily wrap-up is to keep the IRB chair apprised of potential issues and discuss them as they arise. The big question is, "How long will the inspection last?" The answer is anywhere from a couple of days to a couple of weeks, depending on the IRB's workload, the availability of information, and the extent of adverse findings.

After the inspection, the FDA Investigator will write an inspection report, which will go beyond the written list of observations. The Compliance Program details the information needed for the report. The written report goes to FDA headquarters for evaluation. The IRB chair will normally receive communication from FDA headquarters about the inspection. Once the process is closed and no other regulatory or administrative action is anticipated, the FDA will send the IRB chair a copy of the inspection report with minimal redaction of information. However, this process normally takes a couple of months or more.

If there were adverse findings on the inspection, the IRB chair should communicate them to the other members. If things will change as a result of the inspection, the changes should be clearly communicated to clinical investigators so they know what will be new for them.

Consider providing a written response to the FDA concerning any adverse inspectional findings. The FDA does not require a written response unless a warning letter or other type of letter specifically outlines problems and formally asks for a response. If you agree with the inspectional findings and have a proposed solution, let the FDA know. Be aware that if you respond to the investigator's findings, additional issues may arise after headquarters reviews the report, and you may still receive a letter from the FDA. Under such circumstances, it is not a problem from the FDA's standpoint that you have sent a preliminary response that may later turn out to be incomplete.

**Current Events**

Recent FDA inspections have uncovered many problems with IRBs (Table 3). There are multiple examples of each of these failures. It is unsettling to think that in this day and age, these kinds of failures still occur. Part of the problem might be that the FDA has not inspected the IRB in a long time, if ever. Keep in mind, however, that the responsibility for compliance rests with the IRB, not with the FDA. Even if you are not a member of an IRB, your involvement in other aspects of clinical research will eventually convince you that such problems do exist.

The FDA is seeing cases where research is reviewed in the absence of a quorum, voting is done by proxy, or non-members vote. Members are being polled by phone for votes on protocols. The regulations are very clear on the definition of a quorum: a majority of the members of the IRB present at a meeting convened for review of proposed research. People who are polled by phone are not present at a meeting. There are situations and circumstances under which remote communication can be used, but everyone must have the ability to participate in the discussion of the proposed research. Simply polling someone without having them take part in the discussion is not

sufficient. To qualify as a convened meeting, members must receive all of the background information for review in advance of the meeting and have the ability to listen and respond to what is being said.

Votes by proxy are not acceptable. IRB members who have not taken part in the deliberation have no basis for voting. A member might think that the protocol and consent document are the best that he/she has ever seen, but someone else may raise a new concern, not previously considered, that would have an effect on the final vote.

Voting by non-members raises the issues of how you select IRB members; qualifications necessary to be an IRB member and what else they need to learn before they are competent to exercise the responsibility of a board member. A non-member, even if he/she is a former

The FDA has seen failure to prepare and maintain adequate documentation of IRB activities, such as no minutes of certain meetings where approvals were granted; no list of attendees at meetings; and member rosters without dates so inspectors do not know when people became members, how long they were board members, and whether they might have been a member when one of their protocols was considered. These failures all go to the issue of quorum.

In one case, inspectors found correspondence from the IRB to clinical investigators that the investigators had but the IRB could not locate. IRBs are required to keep copies of all documents and correspondence dealing with their activities.

FDA letters to IRBs about significant failures found during inspections may

<p><b>TABLE 3</b>  <b>Current Events Related to FDA Inspections of IRBs</b></p> <ul style="list-style-type: none"> <li>• Failure to prepare written procedures for conducting review of research</li> <li>• Failure to determine that risks to subjects are minimized</li> <li>• Failure to conduct continuing review</li> <li>• Failure to ensure that informed consent included required elements such as unforeseeable risks, alternative treatments, and significant new findings</li> <li>• Consent includes statements such as “new formulation has been shown to be safe” or “FDA may review records due to support of this product”</li> <li>• Failure to review while free from conflict of interest</li> <li>• Research reviewed in absence of a quorum</li> <li>• Failure to prepare and maintain adequate documentation of IRB activities</li> </ul>
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member, is not acceptable to the FDA. Alternate members are acceptable as long as they are rostered as such in advance. The IRB must cover all of the bases in terms of qualifications and diversification of members in order to run a good IRB and provide a meaningful review.

contain one or both of the following statements: “Effective immediately, no new studies are to be approved by your IRB” and “Failure to adequately respond may result in further actions for disqualification of your IRB.” The aim of the agency, and the aim of the IRB chair or member, should be to never get to this point.