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Institutional Review Boards

IRB Compliance Audits—An Underutilized Best Practice

By Donna P. Bergeson

Theodore Roosevelt once said, ''In any moment of decision, the best thing you can do is the right thing, the next best thing is the wrong thing, and the worst thing you can do is nothing.'' Many health care executives and board members do nothing with respect to institutional review board (''IRB'') oversight. Whether inaction is because of the specialized knowledge required to review an IRB, or the perception that the volume of research at the facility is too small to worry about, improperly functioning IRBs can jeopardize the health of patients, the financial health of the institution and the reputation of all caregivers involved.

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Under federal law, every institution engaged in research that is conducted, funded or regulated by a federal department or agency must establish or designate at least one IRB to review and approve research proposals involving human subjects.[1] Almost every hospital I have worked with has had a clinical trial conducted in its facility at one time or another and has an established IRB. Members of the governing boards of those institutions may not be aware that clinical trials occur routinely at their hospital. Where they are aware, few of those institutions have had a compliance review performed to see if the IRB is set up and functioning as required by law. Obtaining an outside review of your IRB is a small investment, with a big payoff.

This article is intended to provide a general background on the requirements of IRBs and encourage governing boards of institutions where clinical research occurs to make the investment in an IRB compliance review. Doing so will ensure that: (1) research subjects in their community who come to their institution for hope and healing are given the protections anticipated by

[1] 45 C.F.R. § 46.101(a).

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law; (2) IRB members (most of whom are volunteers) are equipped with knowledge of how the IRB is functioning and how it should be functioning; (3) supplemental direction can be provided to the institution and its IRB members on their roles in the protection of human subjects; (4) the institution is prepared for an IRB audit conducted by the Food and Drug Administration (''FDA'') or other agency with the power to impose sanctions on the institution; (5) medical care of patients will not be interrupted by an order halting clinical trials; and (6) the fiscal health of the institution will not be jeopardized by the imposition of fines, the withdrawal of its Assurance of Compliance (which is a condition for conducting clinical trials) or other administrative penalties (e.g., debarment).

Academic Institutions

Think it can't happen to your organization? The Department of Health and Human Services (''DHHS'') shut down clinical trials at Duke University in 1999 due to IRB record-keeping deficiencies. Johns Hopkins University, which at the time was the largest recipient of federal research money, halted clinical research following the death of a healthy 24 year-old participating in an asthma study; IRB review of the consent form was a significant issue. More recently, a May 26, 2015, *New York Times* article from a professor at the Center for Bioethics at the University of Minnesota outlined perceived deficiencies in human subject protections at his institution and offered criticism of the IRB process in general.[2] The recent *New York Times* article is likely to spark a flurry of new IRB audits.

Low-Volume IRBs

Not surprisingly, non-academic hospital IRBs have seen an even greater increase in FDA audits over the last decade. A 1998 study provided to the DHHS Inspector General specifically recommended extra focus on ''low-volume'' IRBs, defined as those that conduct fewer than 125 reviews annually.[3] The study showed that low-volume IRBs: (1) review too much, too quickly, with too little expertise; (2) conduct minimal continuing review of approved research; (3) face conflicts that threaten their independence; (4) provide little training for investigators and board members; and (5) *devote little attention to evaluating IRB effectiveness*. It also found substantial risk in requests for quick reviews from commercial sponsors, who may be ''IRB shopping.'' If your facility has a low-volume IRB and has not recently been the subject of an FDA audit, you may be fortunate to get ahead of that curve. You should seize it.

Legal and Regulatory Guidance

Several governmental authorities provide insight into the criteria under which IRBs may be evaluated. Those authorities are all housed within the DHHS and include: the Office for Human Research Protections (''OHRP''); the FDA; and the Office of Inspector General (''OIG''). Further, institutions conducting federally supported human subject research must comply with the Federal Policy for the Protection of Human Subjects (often referred to as the ''Common Rule'').[4] References to these agencies are included throughout this article, but the point of the article is not intended to be lawyerly; it is intended to be practical. For this reason, discussions of the laws and regulations are high-level.

The OIG is the department within the government tasked with overseeing the administration of federal health care programs. Many institutions are familiar with the OIG because of fraud and abuse investigations. The OIG's mission is ''to protect the integrity of Department of Health & Human Services (HHS) programs as well as the health and welfare of program beneficiaries.''[5] As noted on the OIG Web page, this is done through: ''[a] nationwide network of audits, investigations, and evaluations [which] . . . . assists in the development of cases for criminal, civil and administrative enforcement.'' Big brother is out there, and your institution is best advised to look at itself before he does.

IRBs are subject to direct oversight from two governmental agencies. The first is the OHRP, which provides leadership on human research subject protections.[6] The second is the FDA, which ensures the quality and integrity of data for regulatory decisions, as well as protects human research subjects.[7]

The OHRP has published the Institutional Review Board Guidebook (the ''OHRP Guidebook''), which provides the OHRP's interpretation of the Common Rule and other regulations addressing protection of human subjects. While compliance with the Common Rule is mandatory, compliance with the OHRP Guidebook is not. However, the OHRP Guidebook provides useful information on the OHRP's interpretation of the Common Rule, as well as offering guidance on issues typically confronted by institutions conducting clinical research. Accordingly, it is recommended that an evaluation of an IRB follow the framework set forth in the OHRP Guidebook, in addition to the applicable laws and regulations.

As part of its monitoring activities, the FDA reviews the activities of IRBs to ensure they are operating in accordance with their own written procedures, as well as complying with current FDA regulations affecting IRBs. These regulations include 21 C.F.R. Part 50 (Informed Consent), Part 56 (Standards for IRBs), Part 312 (Investigational New Drugs) and Part 812 (Investigational Devices). The FDA places the burden on IRBs to be responsible for determining that:

- risks to human subjects are minimized;
- risks to human subjects are reasonable in relation to the anticipated benefits;
- selection of study subjects is equitable;
- informed consent is sought for every prospective subject; and
- the possibility of coercion or undue influence is minimized.[8]

[2] http://www.nytimes.com/2015/05/26/opinion/the-university-of-minnesotas-medical-research-mess.html?_r=0.

[3] Final Report on Low-Volume Institutional Review Boards (OEI-01-97-00194), dated Oct. 23, 1998.

[4] *See, e.g.*, 45 C.F.R. Part 46.

[5] OIG Website: https://oig.hhs.gov/about-oig/about-us/index.asp.

[6] *See* 45 C.F.R. Part 46.

[7] 21 C.F.R. § 56.115(b).

[8] 21 C.F.R. § 56.111(a); 21 C.F.R. § 50.20

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In November 2005, the OIG released draft Compliance Program Guidance (''CPG'') for recipients of U.S. Public Health Service research awards.[9] The CPG incorporated the same seven elements of an effective compliance program, which the OIG has used for its other CPGs, as well as an eighth element specific to this context. The eighth element is: establishing Roles & Responsibilities & Assigning Oversight Responsibility.[10]

Compliance with CPGs is not mandatory, but the suggestions contained in CPGs often become the industry standard. Moreover, evidence of efforts to comply with CPGs can help mitigate claims of improper intent. Accordingly, IRBs are well advised to evaluate themselves based on the eight elements.

What to Review in an IRB Audit

What are the broad categories that should be reviewed in an IRB audit? I recommend the following:

(1) **Staff and administration**—Is the IRB receiving appropriate administrative support to function properly? Does the IRB have knowledge of and access to an authorized institutional official who can stop research in the event of an emergency?[11] To those readers over the age of 50, an institution is looking for the ''E. F. Hutton'' of the facility. [For those readers who are younger, there used to be a commercial with dozens of folks talking in various conversations in a large and noisy room, but when EF Hutton ''spoke'' everyone would get quiet to listen.]

(2) **Composition of the membership of the IRB**—IRBs are required to have at least five members with varying backgrounds, including considerations of race, cultural heritage and educational backgrounds. Some members must have scientific backgrounds and some non-scientific backgrounds. If an IRB regularly reviews trials with vulnerable populations (e.g., children, prisoners, pregnant women), a member should be knowledgeable about and experienced in working with those subjects.[12]

(3) **Record Keeping of the IRB**—There are six areas of recommended focus with respect to an IRB's record-keeping practices: (1) the roster of IRB members (documenting compliance with the membership composition requirements and the absence of conflicts of interest); (2) written policies and procedures for meetings and the study approval process[13]; (3) study-specific documentation; (4) minutes of IRB meetings; (5) the document retention policy; and (6) a current organizational chart for the IRB.

(4) **Training for IRB members**—The OHRP indicates that IRB members and others charged with responsibility for reviewing and approving research should receive detailed training in the laws, regulations, guidelines and policies applicable to human subjects research.[14] Attending workshops and other educational opportunities focused on IRB functions should be encouraged and supported. In addition, the OIG has indicated that one element of its CPG for research will be conducting effective training and education.[15]

(5) **IRB initial approval of research studies**—A major responsibility of an IRB is to assess the risks and benefits of proposed research.[16] The OHRP and the FDA have specific requirements as to the criteria an IRB must review before approving a research study.[17] These requirements are too detailed for this paper but a compliance review ought to confirm they are understood and documented.

(6) **IRB continuing review of research studies**—The OHRP has provided guidance on the steps an IRB should take in conducting continuing review of ongoing research that is not eligible for expedited review.[18] Specifically, the OHRP suggests that IRB members review a protocol summary and a status report on the progress of the research. The content of the summaries and an exemplar of status reports provided to IRB members should be reviewed for completeness.

(7) **Review of informed consent documents**—One of an IRB's most important activities is evaluating information to be provided to potential subjects in light of the risks and benefits of the proposed research procedures.[19] Earlier in 2015, the FDA issued draft guidance on ''Use of Electronic Informed Consent in Clinical Investigations.'' The guidance should be reviewed and followed.[20] The regulatory requirements for basic informed consent are detailed. Only in certain limited circumstances may an IRB approve a consent procedure which does not contain all of the elements of informed consent or waive the requirement to ob-

[9] 70 Fed. Reg. 71,312 (Nov. 28, 2005).

[10] The CPG also identifies three ''risk areas'' for research programs, but because these areas focus on entities conducting research (rather than IRBs) they will not be addressed in this article. The three risk areas include: (1) Time and Effort Reporting, (2) Properly Allocating Charges to Award Projects and (3) Reporting Financial Support From Other Sources.

[11] OHRP Guidebook, Chapter 1, Administration of the Institutional Review Board, Institutional Responsibilities, The Authorized Institutional Official.

[12] OHRP Guidebook, Chapter 1, Administration of the Institutional Review Board, Membership; 45 C.F.R. § 46.107; 21 C.F.R. § 56.107.

[13] Policies and procedures should provide a framework for periodically reviewing the conduct of research by investigators. They should not only address the manner in which an IRB will conduct its review, but should also address the reporting of any proposed changes in research activities or unanticipated problems. 45 C.F.R. §§ 46.103(b)(4)-(5).

[14] OHRP Guidebook Chapter 1, Administration of the Institutional Review Board, Institutional Responsibilities, Other Institutional Personnel.

[15] 68 Fed. Reg. 52,783.

[16] OHRP Guidebook, Chapter 3, Basic IRB Review, Risk/Benefit Analysis.

[17] 45 C.F.R. § 46.111(a); 21 C.F.R. § 56.111(a).

[18] OHRP Guidance on IRB Continuing Review of Research, Nov. 10, 2010.

[19] OHRP Guidebook, Chapter 3, Basic IRB Review, Informed Consent, Adequacy of Content.

[20] The guidance document is available on the FDA's website: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM436811.pdf.

tain informed consent.[21] Informed consent must be documented on a form that is approved by the IRB.[22]

Conclusion

Confirming that an institution has a properly functioning IRB is good for the health of patients, the financial health of the institution and the reputation of all caregivers. Governing board members and hospital executives should take the advice of Theodore Roosevelt and not let inaction be construed to be their decision. A properly functioning IRB is well worth the small investment of a regulatory compliance review. It will further demonstrate the hospital board's, and management's, fulfillment of their fiduciary duties and thereby protect those individuals from claims of personal liability.

[21] 45 C.F.R. §§ 46.116(c) and (d).
[22] 45 C.F.R. § 46.117(a); 21 C.F.R. § 50.27(a).

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