
Institutional Review Board Guidebook

*** CHAPTER I *** **INSTITUTIONAL ADMINISTRATION**

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A. JURISDICTION OF THE INSTITUTIONAL REVIEW BOARD

The IRB is an administrative body established to protect the rights and welfare of human research subjects recruited to participate in research activities conducted under the auspices of the institution with which it is affiliated. The IRB has the authority to approve, require modifications in, or disapprove all research activities that fall within its jurisdiction as specified by both the federal regulations and local institutional policy. Research that has been reviewed and approved by an IRB may be subject to review and disapproval by officials of the institution. However, those officials may not approve research if it has been disapproved by the **IRB** [Federal Policy §____.112].

The IRB also functions independently of but in coordination with other committees. For example, an institution may have a research committee that reviews protocols to determine whether the institution should support the proposed research. The IRB, however, makes its independent determination whether to approve or disapprove the protocol based upon whether or not human subjects are adequately protected.

Whenever the IRB reviews a protocol, an initial question is whether the IRB has jurisdiction over approval of the research. That is, the IRB must ask, "Is the research subject to IRB review?" The federal regulations apply "to all research involving human subjects conducted, supported, or otherwise subject to regulation by any federal department or agency" that has adopted the human subjects regulations [Federal Policy §____.101(a)].

The first two questions the IRB faces is whether the activity involves *research*, and second, whether it involves *human subjects*. **Research** is defined by the regulations as "a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge" [Federal Policy §____.102(d)]. **Human subjects** are defined by the regulations as "living individual(s) about whom an investigator (whether professional or student) conducting research obtains (1) data through intervention or interaction with the individual, or (2) identifiable private information" [Federal Policy §____.102(f)]. (Section 102(f) goes on to define the meaning of such terms as "intervention" and "private information.")

In addition, some research that involves human subjects may be exempt from the regulations requiring IRB review [Federal Policy §____.101(b)]. Examples include educational testing and survey procedures where no identifying information will be recorded that can link subjects to the data, and disclosure of the data could not reasonably place the subjects at risk of civil or criminal liability or be damaging to the subjects' financial standing, employability, or reputation; and research that involves the

use of existing data, documents, or specimens, where no identifying information will be recorded that can link subjects to the data.

Jurisdictional questions arise, however, in that the regulations also require that, as part of their Assurances, institutions agree to protect the welfare of all human subjects involved in research, whether or not the research is conducted or supported by a federal department or agency [Federal Policy § __.103(b)(1)]. While the regulations further specify that this requirement "need not be applicable to any research exempted...under § __.101(b)," many institutions' human subjects policies provide that all research, even research that is exempt from review under the federal regulations, is to be reviewed by the IRB. In such cases, the IRB has jurisdiction over all human subjects research, thereby providing broader protection for subjects than that required by the regulations. It is crucial that IRBs keep in mind that their authority to approve, require modifications in, or disapprove research derives from both federal law and institutional policy.

Research that has been reviewed and approved by an IRB may be subject to further review and disapproval by officials of the institution. Those officials may not, however, approve research if it has been disapproved by the IRB [Federal Policy § __.112]. Furthermore, approved research is subject to continuing IRB review and must be reevaluated at least annually (and more frequently, as specified by the IRB) [Federal Policy § __.109(e)].

Research vs. Therapy. The fact that much biomedical research is conducted for the purpose of evaluating new therapies or treatments leads to two problems for IRBs. The first is to some degree a problem of IRB jurisdiction; the second is a problem of risk/benefit assessment.

The distinction between research and treatment can become blurred in patient care settings, as well as in some educational and training settings. This distinction raises questions of IRB jurisdiction over the research: Is the proposed activity one that requires IRB review (pursuant either to federal regulations or institutional policy)? Research itself is not therapeutic; for ill patients, research interventions may or may not be beneficial. Indeed, the purpose of evaluative research is to determine whether the test intervention is in fact therapeutic. The support of an activity by a research grant may sometimes provide a practical, if somewhat artificial, operational answer to the question of whether or not that activity is research. IRBs that review only activities whose review is mandated because of the source of funding (*e.g.*, by DHHS regulations 45 CFR 46), can be confident that the intent of the activity is research rather than therapeutic (although subjects may obtain some therapeutic benefit from the research). But an IRB that reviews all research, regardless of the source of support, may sometimes face questions about whether or not a particular activity performed with therapeutic intent is, therefore, research and should be reviewed. Or it may face the difficult question of whether a formal research **protocol** should be developed (and reviewed by the IRB) for a new or non-validated procedure that is being used for therapeutic purposes within the institution. IRBs should be prepared to play such a role; some prominent commentators have pointed out the dangers of allowing new procedures to come into widespread use without having been systematically validated in well-controlled trials.

The second distinction between research and therapies that may pose a problem for IRBs concerns risk/benefit assessments in research on therapies. Often, the risks of a study may seem justified by a therapy provided as part of the study. IRBs should determine, however, whether the anticipated therapeutic benefits would be available to persons who are not participating in a study that presents additional risks. As is discussed in the Guidebook Section on risk/benefit analysis [Chapter 3, Section A], such benefits should not be used to justify risks presented by the research.

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B. ADMINISTRATION OF THE INSTITUTIONAL REVIEW BOARD

ESTABLISHMENT OF THE INSTITUTIONAL REVIEW BOARD

Each institution engaged in research involving human subjects that is supported by a department or agency to which the Federal Policy applies must establish an IRB to review and approve the research. Under the regulations, an institution can also establish more than one IRB, which may be necessary or appropriate, depending on the structure of the institution or the kinds of human subjects research that is performed at that institution. Alternatively, an institution can designate another institution's IRB to review its research upon approval of the appropriate department or agency. If the research is supported by DHHS, such designations must have the prior approval of the Office for Protection from Research Risks (OPRR, an office within NIH). [*See also* Guidebook Chapter 2, "Regulations and Policies."]

MEMBERSHIP

Federal Policy Requirements. The Federal Policy [§ ___.107] provides that IRBs must have at least five members, with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the institution. The IRB must be sufficiently qualified through the experience and expertise of its members and the diversity of their backgrounds, including considerations of their racial and cultural heritage and their sensitivity to issues such as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects.

In addition to possessing the professional competence necessary to review specific research activities, the IRB must be able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice. The IRB must therefore include persons knowledgeable in these areas. No IRB, however, may consist entirely of members of one profession.

If an IRB regularly reviews research that involves a vulnerable category of subjects, such as children, prisoners, pregnant women, or handicapped or mentally disabled persons, the IRB must consider the inclusion of one or more individuals who are knowledgeable about and experienced in working with these subjects. Department of Education (ED) regulations require, in addition, that when an IRB reviews research for one of its programs that purposefully requires inclusion of handicapped children or mentally disabled persons as research subjects, the IRB must include at least one person primarily concerned with the welfare of these subjects [34 CFR 350.3(d)(2); 34 CFR 356.3(c)(2)].

The IRB must include at least one member whose primary concerns are in scientific areas and at least one member whose primary concerns are in nonscientific areas. It must also include at least one member who is not otherwise affiliated with the institution and who is not part of the immediate family of a person who is affiliated with the institution.

The IRB must make every nondiscriminatory effort to ensure that it does not consist entirely of men or entirely of women. Selections must not, however, be made on the basis of gender.

An IRB may, in its discretion, invite individuals with competence in special areas to assist in the review of issues which require expertise beyond or in addition to that available on the IRB. These individuals may not vote.

No IRB member may participate in the review of any project in which the member has a conflicting interest, except to provide information requested by the IRB.

A list of current IRB members must be submitted to OPRR and also kept with the IRB's records [Federal Policy §§ ___.103(b)(3) and ___.115(a)(5)]. The list must identify members by name, earned degrees, representative capacity, indications of experience (such as board certifications and licenses) sufficient to describe each member's chief anticipated contributions to IRB deliberations, and any employment or other relationship between each member and the institution (*e.g.*, full-time employee, stockholder, unpaid consultant, or board member). Any changes in IRB membership must be reported to the head of the department or agency supporting or conducting the research, unless the department or agency has accepted the existence of a DHHS-approved Assurance [see Federal Policy § ___.103(a)]. In the latter case, changes in membership are to be reported to OPRR [Federal Policy §§ ___.103(b)(3) and ___.115(a)(5)].

IRB Considerations. An IRB can have as many members as necessary for it to perform its duties effectively. Care should be taken, however, to ensure that it does not become so large that its management becomes cumbersome.

The nonaffiliated member of the IRB should be drawn from the local community-at-large. Ministers, teachers, attorneys, business persons, or homemakers are possible candidates. The person selected should be knowledgeable about the local community and be willing to discuss issues and research from that perspective. Consideration should be given to the type of community from which the institution will draw its research subjects. If the community is rural and agricultural, perhaps a farmer would be appropriate, in addition to a minister and/or attorney. If the community is predominately African-American, Hispanic, or other minority, then it would be advisable to have a member of that particular minority (or those minorities, if there is more than one significant minority population) on the IRB. The nonaffiliated member(s) should not be vulnerable to intimidation by the professionals on the IRB, and their services should be fully utilized by the IRB.

An investigator can be a member of the IRB; however, there is a stipulation that must be adhered to without exception: The investigator-as-member cannot participate in the review and approval process for any project in which he or she has a present or

potential conflict of interest. Where the investigator-member has a conflicting interest, he or she should be present only to provide information requested by the IRB. He or she should be absent from the meeting room during the discussion and voting phases of the review and approval process; IRB minutes should reflect whether or not these requirements have been met.

One of the most important actions to be taken in establishing an IRB is selecting the individual who will function as chair. The IRB chairperson should be a highly respected individual from within or outside the institution, fully capable of managing the IRB and the matters brought before it with fairness and impartiality. The task of making the IRB a respected part of the institutional community will fall primarily on the shoulders of this individual. The IRB must be and must be perceived to be fair and impartial, immune from pressure either by the institution's administration, the investigators whose protocols are brought before it, or other professional and nonprofessional sources.

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RECORD KEEPING

The institution, or when appropriate the IRB, must prepare and maintain adequate documentation of IRB activities [Federal Policy § __.115]. In addition to the written IRB procedures and membership lists required by the Assurance process [Federal Policy § __.103], such documentation must include copies of all research proposals reviewed, minutes of IRB meetings, records of continuing review activities, copies of all correspondence between the IRB and investigators, and statements of significant new findings provided to subjects (as required by Federal Policy § __.116(b)(5)).

Minutes of IRB meetings must be kept in sufficient detail to record the following information: attendance at each meeting; actions taken by the IRB; the vote on actions taken (including the number of members voting for, against, and abstaining); the basis for requiring changes in or disapproving research; and a written summary of the discussion of controverted issues and their resolution [Federal Policy § __.115(a)(2)].

IRB records must be retained for at least three years; records pertaining to research that is conducted must be retained for three years after completion of the research. All records must be accessible for inspection and copying by authorized representatives of the department or agency supporting or conducting the research at reasonable times and in a reasonable manner [Federal Policy § __.115(b)].

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INSTITUTIONAL RESPONSIBILITIES

Each institution engaged in research must establish one or more IRB, or designate one from another institution, to review and approve research involving human subjects performed at its facilities. Before any human subjects research can be conducted, the institution must provide the department or agency a written **Assurance** that it will comply with the requirements of the Policy; the Assurance must be approved by the department or agency; and the institution must certify to the department or agency head that the research has been reviewed and approved by an IRB established in accordance with the requirements of the Policy [Federal Policy § __.103]. Note, however, that the FDA does not require the submission and approval of an Assurance. (See Guidebook Chapter 2, Section B for a comparison FDA and DHHS human subjects regulations.)

Specification of quality standards in the conduct of research is an important function of the institutional leadership. Insistence upon well-conceived and -conducted research should be evident both in written policies and in actions of institutional officials. Research that is conducted so poorly as to be invalid exposes subjects and the institution to unnecessary risk. Approval procedures should be devised such that the institution supports only well-designed and properly executed research.

The Assurance

An institution involved in biomedical or behavioral research should have in place a set of principles and guidelines that govern the institution, its faculty, and staff, in the discharge of its responsibilities for protecting the rights and welfare of human subjects taking part in research conducted at, or sponsored by, the institution, regardless of the source of funding [Federal Policy § __.103(b)(1)]. Assurances applicable to federally supported or conducted research must, at a minimum, contain such a statement of principles, which may include an appropriate existing code, declaration, and/or statement of ethical principles as formulated by the institution. In the United States, most institutions cite *The Belmont Report*. Foreign institutions sometimes cite other codes, such as the Declaration of Helsinki.

This set of principles should be in the form of a document that is readily available to all staff or faculty personnel who have need of it and can be a part of the staff or faculty manual. It should be written in clear, concise, unambiguous language, understandable to its intended audience.

Staff, Space, and Supplies

The parent institution of the IRB should provide the IRB with sufficient meeting space and staff to support the IRB's review and record keeping duties [Federal Policy § ___.103(b)(2)].

Communication

The institutional leadership must assure that open channels of communication are maintained at all levels. It is important that staff, subjects, and other interested parties have a means of communicating information about the conduct of a research project directly to the appropriate institutional officials. It is vital that IRB members, department heads, and other officials with responsibility for oversight of research have open and ready access to the highest levels of authority within the institution.

Institutional Procedures and Guidelines

Federal Policy Requirements. As provided for in its Assurance, an institution must prepare written procedures and guidelines to be followed by the IRB when conducting its initial and continuing review of research, and for reporting its findings and actions to the investigator and the administration of the institution. The procedures must provide guidance for determining which projects will require review more often than annually and which projects require verification from sources other than the investigator that no material changes have occurred since the last IRB review. The guidelines must also delineate procedures for ensuring prompt reporting to the IRB, by the investigator, of proposed changes in a research activity. They must also provide procedures for ensuring that such changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except when necessary to eliminate apparent immediate hazards to the subject [Federal Policy § ___.103(b)(4)].

The institution must also have written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the department or agency head of: (1) any unanticipated problems involving risks to subjects or others, or any serious or continuing noncompliance with the Federal Policy or the requirements or determinations of the IRB; and (2) any suspension or termination of IRB approval [Federal Policy § ___.103(b)(5)].

The Authorized Institutional Official. Within the institution there must be a point of responsibility for the oversight of research and IRB functions. This point should be an official of the institution who has the legal authority to act and speak for the institution, and should be someone who can ensure that the institution will effectively fulfill its research oversight function. The authority can be delegated. The institution's president or chief executive officer (CEO) should appoint or delegate the appointment of the individual. If the CEO does not function as the Authorized Institutional Official, that person should be the equivalent of the director of research and development, a dean or assistant dean, or hospital administrator. Examples of individuals who should not be appointed, since they cannot speak or act for the institution are: department chair, director of oncology, research coordinator, and so forth. The person in this position may have the additional responsibility of selecting the chair of the IRB. Selection of appropriate personnel will assure the protection of the rights and welfare not only of research subjects, but also the institution itself. The designation of responsible officials must therefore be a considered action by the institutional leadership.

Other Institutional Personnel. Training new personnel is a basic responsibility of any institution. In facilities that conduct research, all personnel should be aware of the applicable institutional policies and mechanisms for the approval of research and for reporting problems with research projects in progress. Personnel involved in the conduct of research should receive additional training in institutional expectations and specific regulations pertaining to research. Training designed to enhance the development of high quality proposals should be encouraged. IRB members and others charged with responsibility for reviewing and approving research should receive detailed training in the regulations, guidelines, and policies applicable to human subjects research. Attending workshops and other educational opportunities focused on IRB functions should be encouraged and supported to the extent possible. Training in good research practices and in methods for minimizing risk should be provided. Since research conducted by others may have a bearing on research projects conducted by or at the institution, journals and other research-related materials should be available to staff.

Internal Audits. Internal audit procedures assure the institution's administration that its policies and procedures are being adhered to and that they are proper in scope and content. Evaluation of activities and functions is an accepted management tool,

and the monitoring of institutional high risk areas such as research is good policy. Audits allow the early identification and correction of problems. The institution must ensure that reporting of noncompliance is accomplished and that appropriate follow-up measures are taken [Federal Policy § ___.103]. *See also* Guidebook Chapter 1, Section D, "Compliance/Noncompliance."

POINTS TO CONSIDER

1. Do institutional policies comply with applicable regulations and promote appropriate review and approval?
2. Are the relevant institutional channels of communication sufficiently open?
3. Do adequate procedures for monitoring research and conducting audits of the research process exist?
4. Does the institution adequately provide for the training of personnel in policies and procedures related to research with human subjects?
5. Does the institution support educational activities related to the design, conduct, and approval of research?

APPLICABLE LAWS AND REGULATIONS

Federal Policy § ___.101 [To what does this policy apply?]

Federal Policy § ___.102 [Definitions]

Federal Policy § ___.103 [Assuring compliance with this policy C research conducted or supported by any federal department or agency]

Federal Policy § ___.107 [IRB membership]

Federal Policy § ___.108 [IRB functions and operations]

Federal Policy § ___.109 [IRB review of research]

Federal Policy § ___.110 [Expedited review procedures]

Federal Policy § ___.111 [Criteria for IRB approval of research]

Federal Policy § ___.112 [Review by institution]

Federal Policy § ___.115 [IRB records]

21 CFR 50 [FDA: Protection of human subjects (informed consent)]

21 CFR 56 [FDA: Institutional review boards]

34 CFR 97 [ED: Protection of human subjects]

34 CFR 350.3 [ED: What regulations apply to these programs (IRB membership)]

34 CFR 356.3 [ED: What regulations apply to these programs (IRB membership)]

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C. PRINCIPAL INVESTIGATORS

IRB CONSIDERATIONS

The qualifications of the principal investigator should be considered when reviewing proposals. The investigator's professional development should be taken into account and related to the degree of protocol complexity and risk to human subjects. IRBs may require less experienced research investigators to be sponsored by seasoned researchers. Proposals that require skills beyond those held by the principal investigator should be modified to meet the investigator's skills, have additional qualified personnel added, or be disapproved.

Research investigators shall prepare protocols giving complete descriptions of the proposed research. The research plan must include provisions for the adequate protection of the rights and welfare of prospective subjects and ensure that pertinent laws and regulations are observed. Samples of informed consent documents must be included with protocols. Research investigators are responsible for obtaining informed consent and ensuring that no human subject will be involved in the research prior to obtaining the consent.

The research plan must address quality assurance standards set by the institution. In addition, applicable external standards for quality assurance must be met. External standards are of particular concern for research conducted in clinical facilities. Appropriate reviews for scientific merit must be conducted before the research is approved. Mechanisms for monitoring the progress of the research must be in place.

Research investigators, through their research design, determine whether the proposed research will involve human subjects. When it is not clear whether the research will involve human subjects, investigators should seek assistance from the IRB in making this determination [Federal Policy § __.101(b)(1)-(6), __.118, and __.119]. Some IRBs, for example, require that all research protocols involving human subjects be submitted to the IRB for review. The IRB then determines whether the research is exempted from IRB review under the applicable regulations and institutional policies, and whether full or expedited IRB review is appropriate.

Researchers are responsible for complying with all IRB decisions, conditions, and requirements. Research investigators are responsible for reporting the progress of the research to the IRB and/or appropriate institutional officials as often as and in the manner prescribed by the IRB but no less than once per year [Federal Policy § __.109(e)].

POINTS TO CONSIDER

1. Does the principal investigator have the appropriate qualifications, experience, and facilities to ensure that all aspects of the project and follow-up will be conducted rigorously and with due regard for the safety and well-being of the subjects?
2. Are adequate procedures in place through which the researcher will monitor the project and report problems to the IRB?
3. What is the investigator's past record with regard to approved research?

APPLICABLE LAWS AND REGULATIONS

Federal Policy § __.101 [To what does this policy apply?]

Federal Policy § __.102 [Definitions]

Federal Policy § __.109 [IRB review of research]

Federal Policy § __.111 [Criteria for IRB approval of research]

Federal Policy § __.116 [General requirements for informed consent]

Federal Policy § __.119 [Research undertaken without the intention of involving human subjects]

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D. COMPLIANCE / NONCOMPLIANCE

INTRODUCTION

Two basic approaches exist for ensuring compliance with human subjects regulations. FDA uses a system of inspections and audits; other DHHS components rely prospectively on assurances of compliance that are negotiated with institutions by OPRR. This divergence in approach reflects the respective agencies' mandates: FDA is regulatory (it regulates the pharmaceutical, biologic, and device industry, whether or not those substances or devices are used for research purposes, as well as the marketing and use of investigational drugs); other DHHS agencies, such as NIH, are research-supporting. FDA regulations provide specific administrative action and sanctions for noncompliance [21 CFR 56.120-24], which DHHS regulations [45 CFR 46] do not. [See, however, 45 CFR 46.123(a).] This Section deals primarily with compliance under DHHS regulations.

An **Assurance** is a written document negotiated with OPRR on behalf of the Secretary, HHS, that sets forth the means by which an institution will comply with DHHS regulations. Assurances are given as a condition of receipt of DHHS support for research involving human subjects. An Assurance approved by OPRR commits the institution and its personnel to full compliance with the DHHS human subjects regulations. Assurances are required by §46.103 of the Federal Policy (not adopted by FDA). That Section provides the required contents of the Assurance. [See Guidebook Chapter 2, Section A(iii), "Assurances."] While recognizing both individual and institutional responsibility for compliance with the regulations, OPRR generally negotiates Assurances only with institutions, which are ultimately responsible for ensuring that the regulatory requirements are met. Investigators and IRBs, however, also retain responsibility for complying with the regulations.

IRB CONSIDERATIONS

The Regulations

DHHS regulations (and those of any other department or agency that has adopted the Federal Policy) require that institutions follow written procedures for ensuring that serious or continuing noncompliance with the regulations or the requirements or determinations of the IRB will be reported to the IRB, appropriate institutional officials, and the head of the department or agency supporting the research [45 CFR 46.103(b)(5)]. FDA requires that such reports be made to the IRB, appropriate institutional officials, and the FDA [21 CFR 56.108(b)]. Each institution is responsible for establishing the mechanism through which instances of noncompliance will be reported to the department or agency. FDA interprets §56.108(b) to require that the IRB itself notify FDA of instances of noncompliance if such reporting would not otherwise occur [*Federal Register* 56 (June 18, 1991): 28026].

Suggested Internal Methods for Ensuring Compliance

To ensure compliance with the regulations, many institutions adopt internal audit or self-assessment procedures and practices designed to assure proper protocol and consent document preparation, protocol submission, review and approval by the IRB, and timely monitoring of protocol implementation. One example is the use of expiration date stamps on consent documents and protocols to ensure that the federal requirement of at least annual IRB review of each protocol is met. A second example is the use of standardized language, endorsed by the institution, which meets the minimal regulatory requirements and which is customized and elaborated upon by the investigator in creating an appropriate informed consent document.

External Audits and Site Visits

Regulatory compliance is similarly fostered by routine site visits and audits conducted by federal officials. The FDA monitors IRB compliance through a program of regular on-site inspections of IRB minutes and records. OPRR conducts occasional site visits to institutions to assess the adequacy of their procedures for protecting human research subjects. In addition, sponsors of research, such as the National Cancer Institute, and cooperative group research organizations, such as the Eastern Cooperative Oncology Group (ECOG), regularly audit their research performance sites. These audits normally include an examination of IRB minutes and records for conformance with applicable regulations. The results of these audits are shared with OPRR and FDA. On-site assessments are designed principally to instruct and educate.

Investigations Into Alleged Noncompliance

As warranted, both the FDA and OPRR conduct inquiries or investigations into alleged noncompliance with federal regulations. The need for site visits in connection with inquiries and investigations depends upon the seriousness and urgency of the circumstances, and whether on-site involvement is the most effective means of resolving the questions of noncompliance that have been raised.

Federal inquiries and investigations into alleged noncompliance with the regulations are not undertaken lightly. Experience has shown that these efforts are usually initiated in response to credible reports of inappropriate involvement of human subjects in research. Such reports can come from any source: IRB members, investigators, subjects, institutional personnel, or the media.

The FDA follows specific regulatory and administrative procedures regarding its determination of non-compliance, the imposition of sanctions, and appeal mechanisms. [See 21 CFR 56.121-124; FDA Compliance Program Guidance Manual, Chapter 48 - Bioresearch Monitoring - Human Drugs: Institutional Review Board (issued November 1988).]

DHHS regulations do not specify administrative actions for noncompliance with the human subjects regulations, except to state that material failure to comply with the regulations can result in termination or suspension of support for department or agency projects, and that DHHS will take terminations or suspensions of funding due to noncompliance into consideration when making future funding decisions [45 CFR 46.123]. OPRR compliance oversight procedures (called "compliance oversight evaluations") are described in a February 5, 1993 memorandum from the Director of OPRR, which is included in the Guidebook in Appendix 5. In part, the memorandum describes OPRR procedures as follows:

When OPRR initiates a compliance oversight evaluation, appropriate institutional officials are so advised, and they are informed as to the likely administrative course of events. Activities expected of the institution are carefully explained initially and at appropriate times during the course of the evaluation. Except in rare circumstances when sound ethics dictates the need to act immediately, OPRR takes no action against any institution without first affording the institution an opportunity to offer

information which might refute or mitigate adverse determinations. In all cases, appropriate institutional officials are afforded an opportunity to comment in writing before OPRR issues its findings.

Under HHS regulations at 45 CFR 5, documents related to compliance oversight evaluations may be subject to the provisions of the Freedom of Information Act (FOIA). In most cases, such documents are exempt from the disclosure provisions of the FOIA while the evaluation is in progress, and OPRR treats them with confidentiality. However, OPRR routinely advises appropriate [D]HHS officials concerning the status of its evaluations and may be required to inform members of Congress. Most documents related to compliance oversight evaluations become publicly available under the FOIA when OPRR issues its findings.

Under HHS regulations at 45 CFR 5b, records which can be retrieved by an individual's name or other personal identifier are subject to the provisions of the Federal Privacy Act. Information regarding OPRR's compliance oversight activities is maintained only in a system of records identifying the institution under evaluation. Records can be retrieved by institutional name or Assurance number. OPRR maintains no system of records related to compliance oversight activities through which records can be retrieved by individuals' names or other personal identifiers....

OPRR's compliance oversight evaluations may result in one or more of the following outcomes:

- (1) OPRR may determine that protections under an institution's Assurance of Compliance are in compliance with the HHS Regulations or the PHS Policy....
- (2) OPRR may determine that protections under an institution's Assurance of Compliance are in compliance with the HHS Regulations or the PHS Policy...but that recommended improvements to those protections have been identified.
- (3) OPRR may restrict its approval of an institution's Assurance of Compliance. Affected research projects cannot be supported by HHS until the terms of the restriction have been satisfied. Examples of such restrictions include, but are not limited to:
 - (a) suspending the Assurance's applicability relative to some or all research projects until specified protections have been implemented;
 - (b) requiring prior OPRR review of some or all research projects to be conducted under the Assurance;
 - (c) requiring that some or all investigators conducting research under the Assurance receive appropriate human subject or animal welfare education;
 - (d) requiring special reporting to OPRR.
- (4) OPRR may withdraw its approval of an institution's Assurance of Compliance. Affected research projects cannot be supported by any HHS component until an appropriate Assurance is approved by OPRR.
- (5) OPRR may recommend to appropriate HHS officials or PHS agency heads
 - (a) that an institution or an investigator be temporarily suspended or permanently removed from participating in specific projects, and/or
 - (b) that peer review groups be notified of an institution's or an investigator's past noncompliance prior to review of new projects.
- (6) OPRR may recommend to HHS that institutions or investigators be declared ineligible to participate in HHS-supported research (Debarment). If OPRR makes this recommendation, the Debarment process will be initiated in accordance with the procedures specified at 45 CFR 76.

Noncompliance by Investigators, IRBs, and Institutions

Investigators. Research investigators are the most frequent source of noncompliance with human subjects regulations. The most common lapses in investigator compliance include unreported changes in protocols, misuse or nonuse of the informed consent document, and failure to submit protocols to the IRB in a timely fashion. Problems such as these are often caused by communication difficulties. With investigator goodwill, these cases can be resolved by the IRB without jeopardizing the welfare of research subjects.

Occasionally, an investigator will either avoid or ignore an IRB. Such cases present a more serious challenge to the IRB and to the institution. Regardless of investigator intent, unapproved research involving human subjects places those subjects at an unacceptable risk. When unapproved research is discovered, the IRB and the institution should act promptly to halt the research, assure remedial action regarding any breach of regulatory or institutional human subject protection requirements, and address the question of the investigator's fitness to conduct human subject research. Beyond the obvious need to protect the rights and welfare of research subjects, the credibility of the IRB is clearly at stake. In addition, any serious or continuing noncompliance with DHHS human subjects regulations or the determinations of the IRB must be promptly reported to OPRR (or the department or agency head) [Federal Policy § ___.103(b)(5)].

IRBs. IRB noncompliance occurs whenever the IRB deviates from the duties imposed upon it by the federal regulations. Such deviations include the inadequate review of research protocols by failing to ensure that the consent document and process provide sufficient information to allow prospective subjects to make an informed decision whether to participate in the research; failing to ensure that the research design includes adequate monitoring of the data and any additional safeguards necessary to protect the welfare of particularly vulnerable subjects; and failing to conduct continuing review of research at intervals appropriate to the degree of risk. IRBs also breach their regulatory responsibilities by failing to maintain adequate records of IRB business and to hold their meetings with a majority of members present, including a nonscientific member. A demonstrated inability to carry out IRB responsibilities in accordance with DHHS regulations can be cause for the suspension or withdrawal of approval of an institution's Assurance.

Institutions. Although institutions are accountable for the actions of individual investigators and the IRB, institutional noncompliance is more broadly described as a systemic failure of the institution to implement practices and procedures contained in the institution's Assurance. Prime examples are the failure of the institution to ensure that the IRB is appropriately constituted and functions in accordance with the regulations, that the IRB receives appropriate institutional support and staffing, and that investigators meet their obligations to the IRB. Systemic failure to abide by the terms and conditions of an institution's Assurance will result in withdrawal of approval of the Assurance.

APPLICABLE LAWS AND REGULATIONS

Federal Policy for the Protection of Human Subjects

21 CFR 56.108(b) [FDA: IRB functions and operations]

21 CFR 56.120-124 [FDA: Administrative actions for noncompliance]

Federal Register 56 (June 18, 1991): 28026 [FDA]

45 CFR 46.103 [DHHS: Assuring compliance with this policy]

45 CFR 46.123 [DHHS: Early termination of research support]

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SUGGESTIONS FOR FURTHER READING

A. Jurisdiction of the Institutional Review Board

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C. Principal Investigators

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D. Compliance/Noncompliance

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