Division of Compliance Oversight

Office for Human Research Protections (OHRP)

OHRP Compliance Oversight Activities: Significant Findings and Concerns of Noncompliance
10-12-2005

This document provides a list of significant findings that OHRP has made and concerns that have been expressed in compliance oversight determination letters over the last several years. The document no longer includes guidance because the guidance is or will be in guidance documents on the OHRP Policy website. These are examples of language that appear in OHRP compliance oversight determination letters.

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A. INITIAL AND CONTINUING REVIEW

(1) Research Conducted without IRB Review. In accordance with HHS regulations at 45 CFR 46.103(b) and 46.109(a), the IRB must review and approve all non-exempt human subject research covered by an assurance. OHRP finds that certain non-exempt human subjects research was conducted without IRB review.

(2) Failure of IRB to Review HHS Grant Applications. HHS regulations at 45 CFR 46.103(f) require that an institution with an approved assurance shall certify that each application or proposal for research covered by the assurance has been reviewed and approved by the IRB.

> (a) OHRP observed numerous discrepancies between the title, date, and type of IRB approval reported on the face page of grant applications and the relevant documentation in IRB records.
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> (b) In reviewing IRB records, and in discussions with IRB members, IRB administrators, and research investigators, OHRP finds that the IRB consistently fails to review the grant application for proposed research.

(3) IRB Lacks Sufficient Information to Make Determinations Required for Approval of Research. OHRP finds that the IRB, when reviewing protocol applications, often lacks sufficient information to make the determinations required for approval of research under HHS regulations at 45 CFR 46.111. For example, the IRB appears to review only minimal information regarding (a) risks to subjects and how they are minimized; (b) subject recruitment and enrollment procedures; (c) the equitable selection of subjects; (d) provisions to protect the privacy of subjects and maintain the confidentiality of data; and (e) additional safeguards to protect the rights and welfare of subjects who are likely to be vulnerable.

(4) Inadequate IRB Review at Convened Meetings. In accordance with HHS regulations at 45 CFR 46.108(b), review of proposed research must be conducted by the IRB at convened meetings at which a majority of the members of the IRB are present, including at least one member whose primary concerns are in nonscientific areas, except where expedited review is appropriate under HHS regulations at 45 CFR 46.110(b)(2). The minutes of IRB meetings, and discussions with IRB members and administrators, indicate that little substantive review takes place at convened meetings. Most protocols [and amendments] undergoing [initial/continuing] review are neither individually presented nor discussed at a convened meeting by the IRB as a group. Furthermore, OHRP's review of available materials yielded little evidence that IRB approval of research is consistently based on consideration of the determinations required under HHS regulations at 45 CFR 46.111. Specifically, the IRB appears not to consider systematically and rigorously such issues as risks to subjects and how they are minimized, equitable selection of subjects and subject recruitment, privacy and confidentiality protections, and special protections required for vulnerable subjects.

(5) Inadequate Continuing Review. Continuing review of research must be substantive and meaningful. HHS regulations at 45 CFR 46.111 set forth the criteria that must be satisfied in order for the IRB to approve research. These criteria include, among other things,

determinations by the IRB regarding risks, potential benefits, informed consent, and safeguards for human subjects. The IRB must ensure that these criteria are satisfied at the time of both initial and continuing review. The procedures for continuing review by the convened IRB may include a primary reviewer system.

In conducting continuing review of research not eligible for expedited review, all IRB members should at least receive and review a protocol summary and a status report on the progress of the research, including: (i) the number of subjects accrued; (ii) a summary of adverse events and any unanticipated problems involving risks to subjects or others and any withdrawal of subjects from the research or complaints about the research since the last IRB review; (iii) a summary of any relevant recent literature, interim findings, and amendments or modifications to the research since the last review; (iv) any relevant multi-center trial reports; (v) any other relevant information, especially information about risks associated with the research; and (vi) a copy of the current informed consent document and any newly proposed consent document.

At least one member of the IRB (i.e., a primary reviewer) also should receive a copy of the complete protocol including any protocol modifications previously approved by the IRB. Furthermore, upon request, any IRB member also should have access to the complete IRB protocol file and relevant IRB minutes prior to or during the convened IRB meeting. The minutes of IRB meetings should document separate deliberations, actions, and votes for each protocol undergoing continuing review by the convened IRB.

When conducting continuing review of research under an expedited review procedure, the IRB Chair (or designated IRB member(s)) should receive and review all of the above-referenced documentation, including the complete protocol.

OHRP finds that continuing review of research by the IRB was not substantive and meaningful.

(6) Contingent Approval of Research with Substantive Changes and no Additional Review by the Convened IRB. OHRP finds that the IRB frequently approves research contingent upon substantive modifications or clarifications that are directly relevant to the determinations required by the IRB under HHS regulations at 45 CFR 46.111 without requiring additional review by the convened IRB. OHRP notes that when the convened IRB requests substantive clarifications or modifications regarding the protocol or informed consent documents that are directly relevant to the determinations required by the IRB under HHS regulations at 45 CFR 46.111, IRB approval of the proposed research must be deferred, pending subsequent review by the convened IRB of responsive material.

(7) Failure to Conduct Continuing Review at Least Once per Year. HHS regulations at 45 CFR 46.109(e) require that continuing review of research be conducted by the IRB at intervals appropriate to the degree of risk, but not less than once per year. The regulations make no provision for any grace period extending the conduct of the research beyond the expiration date of IRB approval. Additionally, where the convened IRB specifies conditions for approval of a protocol that are to be verified as being satisfied by the IRB Chair or another IRB member designated by the Chair, continuing review must occur no later than one year after the date the protocol was reviewed by the convened IRB, not on the anniversary of the date the IRB Chair

or his or her designee verifies that IRB-specified conditions for approval have been satisfied.

OHRP finds that {extensions beyond the expiration date were granted} OR {the IRB failed to conduct continuing review of research at least once per year}.

The IRB and investigators must plan ahead to meet required continuing review dates. If an investigator has failed to provide continuing review information to the IRB or the IRB has not reviewed and approved a research study by the continuing review date specified by the IRB, the research must stop, unless the IRB finds that it is in the best interest of currently enrolled subjects to continue participating in the research interventions or interactions. The IRB may consider a request for continued participation of all subjects currently enrolled. Enrollment of new subjects cannot occur after the expiration of IRB approval.

(8) IRB Meeting Convened without Quorum (No Nonscientist Present). HHS regulations at 45 CFR 46.108(b) require that, except when an expedited review procedure is used, research be reviewed at convened meetings at which a majority of the members of the IRB are present, including at least one member whose primary concerns are in a nonscientific area. OHRP finds that the IRB meeting on [date] did not include a nonscientist member. Thus, any actions taken at this meeting must be considered invalid. OHRP emphasizes that at any time when no nonscientist member is present during the course of the meeting, the IRB may not take further actions or votes until a nonscientist member returns.

(9) IRB Meeting Convened without Quorum (Lack of a Majority). HHS regulations at 45 CFR 46.108 require that, except when an expedited review procedure is used, the IRB review proposed research at convened meetings at which a majority of the members of the IRB are present. OHRP finds that the IRB failed to meet this requirement for the following IRB meetings: [date], X members present. Thus, any actions taken at these meeting must be considered invalid. OHRP emphasizes that should the quorum fail during a meeting (e.g., those with conflicts being excused, early departures, absence of a nonscientist member), the IRB may not take further actions or votes unless the quorum can be restored.

(10) IRB Members with Conflicting Interest Participated in IRB Review of Research. HHS regulations at 45 CFR 46.107(e) stipulate that no IRB member may participate in the IRB's initial or continuing review of a project in which the member has a conflicting interest, except to provide information requested by the IRB. OHRP finds that, on occasion, IRB members inappropriately participated in the initial and continuing review of protocols for which they had a conflicting interest. OHRP recommends that except when requested by the IRB to be present to provide information, IRB members absent themselves from the meeting room when the IRB reviews research in which they have a conflicting interest, and such should be noted in the IRB meeting minutes.

(11) Continuing Review for Follow up of Subjects in Research Protocols. HHS regulations at 45 CFR 46.109(e) state that an IRB shall conduct continuing review of research covered by this policy at intervals appropriate to the degree of risk, but not less than once per year. Even where (i) the research is permanently closed to the enrollment of new subjects; and (ii) all subjects have

completed all research-related interventions, continuing review is required as long as the research remains active for long-term follow-up of subjects. Furthermore, continuing IRB review of research is required where the remaining research activities are limited to data analysis (see 63 FR 60364-60367, category (8)). OHRP finds that continuing review did not occur in protocols involving follow-up activities.

B. EXPEDITED REVIEW PROCEDURES

(12) Inappropriate Use of Expedited Review Procedures for Initial or Continuing IRB Review. HHS regulations at 45 CFR 46.110(b)(1) limit the use of expedited review procedures to specific research categories published in the Federal Register at 63 FR 60364--60367 (see http://www.dhhs.gov/ohrp/humansubjects/guidance/expedited98.htm). OHRP finds that:

(a) The IRB inappropriately applies expedited review to research that involves minimal risk but does not appear in the categories of research published in the Federal Register.

(b) The IRB inappropriately applies expedited review to research that involves greater than minimal risk.

(13) Inappropriate Use of Expedited Review Procedures for Review of Protocol Changes. HHS regulations at 45 CFR 46.110(b)(2) permit use of expedited procedures for review of minor changes in previously approved research during the period for which approval is authorized. OHRP finds that the IRB has employed expedited procedures to review changes that exceed this limitation. In accordance with HHS regulations at 45 CFR 46.108(b), review of proposed protocol changes must be conducted by the IRB at convened meetings at which a majority of the members of the IRB are present, including at least one member whose primary concerns are in nonscientific areas, except where expedited review is appropriate under HHS regulations at 45 CFR 46.110(b)(2).

(14) Failure to Advise IRB Members of Expedited Approvals. HHS regulations at 45 CFR 46.110(c) require that all IRB members be advised of research proposals which have been approved under an expedited review procedure. OHRP finds that IRB members were not advised of (a) research protocols approved at time of initial or continuing review under an expedited review procedure, or (b) minor changes in research protocols approved under an expedited review procedure.

C. REPORTING OF UNANTICIPATED PROBLEMS, NONCOMPLIANCE, SUSPENSIONS, AND TERMINATIONS,

(15) Failure to Report Unanticipated Problems, Noncompliance, Suspensions, and Terminations, to IRB, Institutional Officials, and OHRP. OHRP finds that the following [unanticipated

problems involving risks to subjects or others/serious or continuing noncompliance/suspensions or terminations of IRB approval] were not reported to [appropriate institutional officials/the IRB/OHRP/the head of the sponsoring Federal department or agency] as required by HHS regulations at 45 CFR 46.103(a) and 46.103(b)(5): [ ]

D. IRB REVIEW OF PROTOCOL CHANGES

(16) Failure of IRB to Review Protocol Changes. HHS regulations at 45 CFR 46.103(b)(4)(iii) require that the IRB review and approve all proposed changes in a research activity, during the period for which IRB approval has already been given, prior to initiation of such changes, except when necessary to eliminate apparent immediate hazards to the subjects. OHRP finds {no documentation that the IRB reviewed and approved the following protocol changes prior to their initiation:}OR {that the following protocol changes were implemented without IRB approval:}

(17) Inadequate IRB Review of Protocol Changes. OHRP is concerned about the adequacy of the IRB's procedure for reviewing protocol modifications. In some cases, the IRB Chair or designated IRB reviewer approved such modifications in the absence of a complete description of the proposed changes.

E. APPLICATION OF EXEMPTIONS

(18) Inappropriate Application of Exempt Categories of Research. HHS regulations at 45 CFR 46.101(b) delineate six specific categories of exempt activities. OHRP finds that the institution has applied an exemption to research activities that exceed these categories. OHRP recommends that documentation for all exemptions include citation of the specific category justifying the exemption.

(19) Inappropriate Application of Exemption 4. HHS regulations at 45 CFR 46.101(b)(4) exempt activities involving existing data, documents, records, or specimens. OHRP notes that such materials must already exist at the time the research is proposed. OHRP finds instances where this exemption was applied to activities involving prospective collection of such materials.

(20) Inappropriate Application of Exemption 2 for Research Involving Children. OHRP emphasizes that the exemption at 45 CFR 46.101(b)(2) for research involving survey or interview procedures or observations of public behavior does not apply to research covered by 45 CFR Part 46, subpart D (Additional Protections for Children Involved as Subjects in Research), except for research involving observation of public behavior when the investigators do not participate in the activities being observed. OHRP finds that exemption 2 was inappropriately applied to research involving children.

(21) Inappropriate Application of Exemption 5 for "Public Benefit" Projects. The following criteria (see 48 FR 9266-9270) must be satisfied to invoke the exemption for research and demonstration projects examining "public benefit or service programs" as specified under HHS regulations at 45 CFR 46.101(b)(5): (a) the program under study must deliver a public benefit (e.g., financial or medical benefits as provided under the Social Security Act) or service (e.g., social, supportive, or nutrition services as provided under the Older Americans Act); (b) the research or demonstration project must be conducted pursuant to specific federal statutory authority; (c) there must be no statutory requirement that the project be reviewed by an Institutional Review Board (IRB); and (d) the project must not involve significant physical invasions or intrusions upon the privacy of participants (see 12/97 OPRR Guidance at http://www.dhhs.gov/ohrp/humansubjects/guidance/exmpt-pb.htm). This exemption is for projects conducted by or subject to approval of Federal agencies, and is most appropriately invoked with authorization or concurrence by the funding agency. OHRP finds that this exemption was inappropriately applied for the following research: [ ]

F. INFORMED CONSENT

(22) Failure to Obtain Legally Effective Informed Consent. HHS regulations at 45 CFR 45.116 state that, except as provided elsewhere in the regulations, no investigator may involve a human being as a subject in research covered by the regulations unless the investigator has obtained the legally effective informed consent of the subjects or the subject's legally authorized representative. OHRP finds that the investigator initiated human subject research without meeting this requirement.

(23) Failure to Document Informed Consent. HHS regulations at 45 CFR 46.117(a) require that informed consent be documented by the use of a written consent form approved by the IRB and that is signed by the subject, or the subject's legally authorized representative, unless the IRB waives this requirement. OHRP finds that informed consent was not documented by a written consent form signed by the subject(s) for this research.

(24) Deficient Informed Consent Documents (ICDs) in General. HHS regulations at 45 CFR 46.116(a) delineate specific elements required for informed consent. OHRP found instances where (a) required elements were omitted; and (b) there were discrepancies between the protocol application and the informed consent documents regarding the purpose, risks, and benefits of the research.

(25) Inadequate ICD for Specific Research/Lack of Required Elements. OHRP finds that the informed consent documents reviewed and approved by the IRB between [date X] and [date Y] for [study Z] failed to [include and/or adequately address] the following elements required by HHS regulations at 45 CFR 46.116(a):

(a) Section 46.116(a)(1): (i) A statement that the study involves research; (ii) an explanation of the purposes of the research (i.e., [summary of purpose]); (iii) the expected duration of the subject's participation; and (iv) a complete description of the procedures to be followed, and identification of any procedures which are experimental (i.e., [procedures not described]).

(b) Section 46.116(a)(2): A description of any reasonably foreseeable risks and discomforts (i.e., [risks and discomforts not described]).

(c) Section 46.116(a)(3): A description of any benefits to the subject or others that may reasonably be expected from the research.

(d) Section 46.116(a)(4): A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject (e.g., [alternatives which should be described]).

(e) Section 46.116(a)(5): A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained.

(f) Section 46.116(a)(6): For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.

(g) Section 46.116(a)(7): An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights (should include someone other than the investigator), and whom to contact in the event of a research-related injury to the subject.

(h) Section 46.116(a)(8): A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

(26) Inadequate ICD for Specific Research/Lack of Additional Elements. OHRP finds that it would have been appropriate for the informed consent documents to include the following additional elements in accordance with HHS regulations at 45 CFR 46.116(b):

(a) Section 46.116(b)(2): Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent.

(b) Section 46.116(b)(4): The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.

(c) Section 46.116(b)(5): A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue

participation will be provided to the subject.

(27) ICD Language too Complex. HHS regulations at 45 CFR 46.116 require that informed consent information be in language understandable to the subject or the subject's legally authorized representative. OHRP is concerned that the informed consent document approved by the IRB for this study appeared to include complex language that would not be understandable to all subjects.

(28) Exculpatory Language in ICDs. HHS regulations at 45 CFR 46.116 prohibit any exculpatory language in informed consent through which the subject is made to waive, or appear to waive, any of the subject's legal rights. OHRP finds the following language in the IRB-approved informed consent documents to be exculpatory: [cite language].

(29) Standard Clinical Consent Documents Lack Required Elements of Informed Consent. OHRP notes that standard clinical consent documents rarely include all the elements required under HHS regulations at 45 CFR 46.116. Reliance on such documents for research generally requires formal waiver of consent requirements in accordance with 45 CFR 46.116(d). OHRP finds no documentation of such waiver in protocols for which clinical consent was accepted in lieu of an IRB-approved research consent document.

(30) Inappropriate Boilerplate ICDs. OHRP is concerned that the boilerplate informed consent document is difficult to understand and contains information that may be irrelevant for certain research.

(31) Enrollment Procedures did not Minimize Possibility of Coercion or Undue Influence. OHRP finds that the procedures for enrolling subjects failed to minimize the possibility of coercion or undue influence as required by HHS regulations at 45 CFR 46.116.

G. IRB MEMBERSHIP, EXPERTISE, STAFF, SUPPORT, AND WORKLOAD

(32) Lack of Diversity of IRB Membership. OHRP is concerned that the current IRB membership appears to lack the diversity, including consideration of race, gender, and cultural backgrounds and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects, as required under HHS regulations at 45 CFR 46.107(a).

(33) Lack of IRB Expertise Regarding Research Involving Children. HHS regulations at 45 CFR 46.107(a) require that an IRB which regularly reviews research involving a vulnerable category of subjects consider inclusion of one or more individuals who are knowledgeable about and experienced in working with these subjects. OHRP finds that the volume of research involving children reviewed by the IRB warrants inclusion of such an individual.

(34) Lack of Prisoner/Prisoner Representative for IRB Review of Research Involving Prisoners.

HHS regulations at 45 CFR 46.304 have specific requirements for IRB membership when reviewing research involving prisoners. Specifically, at least one member of an IRB that reviews the research shall be a prisoner, or a prisoner representative with appropriate background and experience to serve in that capacity. When the convened IRB reviews research involving prisoners (including initial review, continuing review, review of protocol modifications, and review of unanticipated problems involving risks to subjects or others), the prisoner or prisoner representative must be present as a voting member. OHRP finds that the IRB failed to meet this requirement when reviewing research projects involving prisoners.

(35) IRB Chair and Members Lack Sufficient Understanding of HHS Regulations. OHRP is concerned that the IRB Chair and members appear to lack a detailed understanding of the specific requirements of the HHS regulations for the protection of human subjects. As a result, IRB determinations have sometimes deviated from these requirements.

(36) Designation of an Additional IRB under an Assurance without Prior OHRP Approval. HHS regulations at 45 CFR 46.103(b) state, in part, that assurances applicable to federally supported or conducted research shall include designation of one or more IRBs established in accordance with the requirements of the regulations, and for which provisions are made for meeting space and sufficient staff to support the IRB's review and recordkeeping duties.

The institution's assurance presently designates [a single] IRB[s]. Designation of additional IRBs under the assurance requires prior notification of and approval by OHRP. OHRP finds that the institution has established an additional IRB that reviews research covered by its assurance without such approval.

(37) Inadequate IRB Resources. HHS regulations at 45 CFR 46.103(b)(2) require that institutions provide meeting space and sufficient staff to support the IRB's review and recordkeeping duties. OHRP is concerned that (a) the IRB administrative staff lacks resources sufficient to conduct sensitive IRB duties; and (b) the level of staff support provided to the IRB appears to be insufficient. It is OHRP's experience that the volume of human subjects research conducted by the institution warrants [a full-time IRB administrator at the professional level/additional IRB staff members].

(38) Overburdened IRB. OHRP is concerned that items (X)-(Y) above may be indicative of an IRB overburdened by the large volume of research for which it has oversight responsibility. It is OHRP's experience that such a large volume of human subjects research warrants more than one fully functional IRB.

(39) Lack of IRB Knowledge of Local Research Context. HHS regulations at 45 CFR 46.103(d) require that the adequacy of Institutional Review Boards (IRBs) be evaluated in light of the anticipated scope of the institution's research activities, the types of subject populations likely to be involved, . . . and the size and complexity of the institution. The regulations further require at 45 CFR 46.107(a) that IRBs be (a) sufficiently qualified through . . . the diversity of the members, including consideration of race, gender, and cultural backgrounds and sensitivity to

such issues as community attitudes, to promote respect for its advice and counsel; and (b) able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice. Institutions have a profound responsibility to ensure that all IRBs designated under an OHRP-approved Assurance possess sufficient knowledge of the local research context to satisfy these requirements. OHRP finds that the IRB did not have the background and expertise to review the above-referenced research based on its failure to include members with sufficient understanding of the cultural conditions, including the social, economic, and political status, of the subject population. For detailed guidance on appropriate mechanisms for ensuring that the IRB has adequate knowledge of the local research context, please see:
http://www.dhhs.gov/ohrp/humansubjects/guidance/local.htm

H. DOCUMENTATION OF IRB ACTIVITIES, FINDINGS, AND PROCEDURES

(40) Inadequate IRB Records. OHRP finds that IRB protocol records fail to include all the information stipulated at 45 CFR 46.115(a)(1), (3), (4), and (7).

(41) Inadequate IRB Minutes. HHS regulations at 45 CFR 46.115(a)(2) require that minutes of IRB meetings be in sufficient detail to show attendance at the meetings; actions taken by the IRB; the vote on these actions 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. OHRP finds that IRB minutes [often] failed to meet these requirements. Furthermore, OHRP notes that IRB actions were not documented separately for each individual protocol undergoing initial or continuing review.

(42) Poorly Maintained IRB Files. HHS regulations at 45 CFR 46.115(a) require that the institution prepare and maintain adequate documentation of IRB activities. In numerous instances among the IRB files examined by OHRP, it was difficult to reconstruct a complete history of all IRB actions related to the review and approval of the protocol. In some instances, OHRP could not determine what the IRB actually approved.

(43) Failure of IRB to Determine That Criteria for IRB Approval Are Satisfied. HHS regulations at 45 CFR 46.111(a) state that, in order to approve research covered by the regulations, the IRB shall determine that certain requirements are satisfied. OHRP finds that for some research the IRB failed to determine that the following requirements were satisfied:

(1) Risks to subjects are minimized.

(2) Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result.

(3) Selection of subjects is equitable.

(4) Informed consent will be sought from each prospective subject or the subjects's legally authorized representative.

(5) Informed consent will be appropriately documented.

(6) When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.

(7) When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

(44) Failure of IRB to Document Consideration of Additional Safeguards for Vulnerable Subjects. HHS regulations at 45 CFR 46.111(b) require the IRB to ensure that additional safeguards have been included to protect the rights and welfare of vulnerable subjects when research is conducted involving these subjects. OHRP finds that IRB records failed to demonstrate consistently the consideration of such safeguards.

(45) Failure of IRB to Make Required Findings When Reviewing Research Involving Children. HHS regulations at 45 CFR 46.404-407 require specific findings on the part of the IRB for approval of research involving children. OHRP's discussions with IRB members and its review of IRB documents reveal [no, or little] evidence that the IRB consistently makes the required findings when reviewing research involving children.

(46) Failure of IRB to Make Required Findings When Reviewing Research Involving Prisoners. HHS regulations at 45 CFR 46.305-306 require specific findings on the part of the IRB for approval of research involving prisoners. OHRP's discussions with IRB members and its review of IRB documents reveal [no, or little] evidence that the IRB makes the required findings when reviewing such research.

(47) Failure of IRB to Make and Document Required Findings for Waiver of Informed Consent. HHS regulations at 45 CFR 46.116(d) require that the IRB find and document four specific criteria when approving waiver or alteration of some or all of the required elements of informed consent. OHRP's discussions with IRB members and its review of IRB documents reveal no evidence that the IRB consistently satisfies these requirements.

(48) Failure to Make Required Findings for IRB Waiver of a Signed Informed Consent Document. HHS regulations at 45 CFR 46.117(c) require specific findings on the part of the IRB for waiver of the usual requirements for the investigator to obtain a signed consent form from all subjects. OHRP's discussions with IRB members and its review of IRB documents reveals [no, or little] evidence that the IRB makes the required findings when approving such waivers.

(49) Lack of Appropriate Written IRB Procedures. OHRP finds that the institution does not have

written IRB procedures that adequately describe the following activities, as required by HHS regulations at 45 CFR 46.103(a) and 46.103(b)(4) and (5):

> (a) The procedures which the IRB will follow for conducting its initial review of research.
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> (b) The procedures which the IRB will follow for conducting its continuing review of research.
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> (c) The procedures which the IRB will follow for reporting its findings and actions to investigators and the institution.
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> (d) The procedures which the IRB will follow for determining which projects require review more often than annually.
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> (e) The procedures which the IRB will follow for determining which projects need verification from sources other than the investigators that no material changes have occurred since previous IRB review.
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> (f) The procedures which the IRB will follow for ensuring prompt reporting to the IRB of proposed changes in a research activity, and 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.
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> (g) The procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, any department or agency head, and OHRP of: (a) any unanticipated problems involving risks to subjects or others; (b) any serious or continuing noncompliance with 45 CFR part 46 or the requirements or determinations of the IRB; and (c) any suspension or termination of IRB approval.

(50) Inadequate Procedures for Oversight of Repository Activities. OHRP notes that the institution is engaged in several tissue banking or repository activities. These activities require the IRB to make determinations concerning (i) the regulatory status and appropriate use of stored biologic samples, and (ii) the informed consent process for research using such samples. OHRP is concerned that the IRB has not developed policies and procedures for oversight of repository activities that ensure compliance with HHS regulations at 45 CFR part 46 (see OHRP guidance regarding repositories, 11/97 at http://www.dhhs.gov/ohrp/humansubjects/guidance/reposit.htm).

(51) Inadequate Procedure for Reporting and Review of Unanticipated Problems. OHRP is concerned about the adequacy of the IRB's procedures for ensuring prompt reporting, review, and evaluation of unanticipated problems involving risks to subjects or others.

(52) Failure to Obtain an Assurance for Engaged Institutions. HHS regulations at 45 CFR 46.103(a) require that each institution "engaged" in human subjects research provide OHRP with a satisfactory assurance to comply with the regulations, unless the research is exempt under 45 CFR 46.101(b). (Please see OHRP guidance at http://www.dhhs.gov/ohrp/humansubjects/assurance/engage.htm)

An institution becomes "engaged" in human subjects research when its employees or agents (i) intervene or interact with living individuals for research purposes; or (ii) obtain individually identifiable private information for research purposes [45 CFR 46.102(d),(f)].

OHRP finds that [X institution] was engaged in human subject research under project # [Y] and the site did not obtain an OHRP-approved assurance for this research. If the above-mentioned project is ongoing, involvement of [X institution] in human subject research activities under the above-referenced HHS award must be suspended until OHRP approves an assurance.

(53) Inadequate Retention of IRB Records. HHS regulations at 45 CFR 46.115(b) require that IRB records be retained for at least 3 years, and records relating to research which is conducted be retained for at least 3 years after completion of the research. All records must be accessible for inspection and copying by authorized representatives of HHS at reasonable times and in a reasonable manner. OHRP finds that the institution failed to retain [IRB records/records relating to research] for at least 3 years after completion of the research.