Compliance Oversight Branch
Division of Human Subject Protections
Office for Human Research Protections (OHRP)

OHRP Compliance Activities: Common Findings and Guidance - 7/10/2002

CLICKABLE INDEX

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

Common OHRP Findings of Noncompliance

Additional OHRP Guidance

G. DOCUMENTATION OF IRB ACTIVITIES, FINDINGS, AND PROCEDURES

Common OHRP Findings of Noncompliance

Additional OHRP Guidance

H. MISCELLANEOUS OHRP GUIDANCE

A. INITIAL AND CONTINUING REVIEW

Common OHRP Findings of Noncompliance

(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 found that certain human subject 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 found 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.
>
> (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 is concerned that when reviewing protocol applications, the IRB often appears to lack 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) subject recruitment and enrollment procedures; (b) the equitable selection of subjects; (c) provisions to protect the privacy of subjects and maintain the confidentiality of data; and (d) additional safeguards to protect the rights and welfare of subjects who are likely to be vulnerable.

(4) Inadequate IRB Review at Convened Meetings. The minutes of IRB meetings, and our discussions with IRB members and administrators, indicate that little substantive review takes place at convened meetings. Most protocols undergoing [initial/continuing] review are neither individually presented nor discussed at a convened meeting by the IRB as a group. Furthermore, OHRP's inspection of available materials yielded scant evidence that IRB approval of research is consistently based on consideration of the determinations required under HHS regulations at 45 CFR 46.111. In specific, the IRB appears not to consider systematically and rigorously such issues as 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 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 reviewing 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 without requiring additional review by the convened IRB. OHRP recommends the following guidelines in such cases: (a) 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 should be **deferred**, pending subsequent review by the convened IRB of responsive material. (b) Only when the convened IRB stipulates specific revisions requiring simple concurrence by the investigator may the IRB Chair or another IRB member designated by the Chair subsequently approve the revised research protocol on behalf of the IRB under an expedited review procedure.

(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 and 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 more 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 found numerous instances in which {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 interests of individual subjects to continue participating in the research interventions or interactions. Enrollment of new subjects cannot occur after the expiration of IRB approval.

(8) IRB Meeting Convened without Quorum (Nonscientist Absent). 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 [date] IRB meeting did not include a nonscientist member. Thus, any actions taken at this meeting must be considered invalid. OHRP emphasizes that 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 found 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 found instances in which 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.

Additional OHRP Guidance

(11) Requirement for Review of Research by the IRB at Convened Meetings. In accordance with HHS regulations at 45 CFR 46.108(b), initial and continuing reviews of 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 (i.e., a quorum), except where expedited review is appropriate under HHS regulations at 45 CFR 46.110(b)(1) for the categories of research listed in the Federal Register of November 9, 1998 (see 63 FR 60364-60367 at http://ohrp.osophs.dhhs.gov/humansubjects/guidance/expedited98.htm). Approval of research is by a majority vote of this quorum.

(12) Loss of Quorum During IRB Meeting. A quorum for IRB meetings is a majority of the IRB's voting members, including at least one member whose primary interests are in nonscientific areas (see 45 CFR 46.108(b)). Approval of research is by majority vote of those present. Should the quorum fail during a meeting (e.g., loss of a majority through recusal of members with conflicting interests or early departures, or absence of a nonscientist member), the IRB may not take further actions or votes unless the quorum can be restored.

(13) IRB Review in Emergency Situations. HHS regulations do not permit human subject research activities to be started, even in an emergency, without prior IRB review and approval (see 45 CFR 46.103(b) and 46.116(f) and OHRP guidance at http://ohrp.osophs.dhhs.gov/humansubjects/guidance/hsdc91-01.htm). When emergency medical care is initiated without prior IRB review and approval, the patient may not be considered a research subject under 45 CFR Part 46. Such emergency care may not be claimed as research, nor may any data regarding such care be included in any report of a prospectively conceived research activity. When emergency care involves investigational drugs, devices, or biologics, U.S. Food and Drug Administration (FDA) requirements must be satisfied.

(14) Initial Review Materials. In conducting the initial review of proposed research, IRBs must obtain information in sufficient detail to make the determinations required under HHS regulations at 45 CFR 46.111. Materials should include the full protocol, a proposed informed consent document, any relevant grant application(s), the investigator's brochure (if one exists), and any recruitment materials, including advertisements intended to be seen or heard by potential subjects. Furthermore, for HHS-supported multicenter clinical trials, the IRB should receive and review a copy of the HHS-approved sample informed consent document and the complete HHS-approved protocol, if they exist. Unless a primary reviewer system is used, all members should receive a copy of the complete documentation. These materials should be received by members sufficiently in advance of the meeting date to allow review of this material.

(15) Primary Reviewer Systems. If the IRB uses a primary reviewer system, the primary reviewer(s) should do an in-depth review of all pertinent documentation (see previous paragraph). All other IRB

members should at least receive and review a protocol summary (of sufficient detail to make the determinations required under HHS regulations at 45 CFR 46.111), the proposed informed consent document, and any recruitment materials, including advertisements intended to be seen or heard by potential subjects. In addition, the complete documentation should be available to all members for review.

(16) Continuing Review for Follow up in Research Protocols. For research where (i) the research is permanently closed to the enrollment of new subjects; (ii) all subjects have completed all research-related interventions, continuing IRB review is required as long as the research remains active only 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)).

B. EXPEDITED REVIEW PROCEDURES

Common OHRP Findings of Noncompliance

(17) 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. 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.

(18) 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 to 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.

(19) Failure to Advise IRB Members of Expedited Approvals. 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, as required by HHS regulations at 45 CFR 46.110(c).

Additional OHRP Guidance

(20) Documentation for Initial and Continuing Expedited Review. OHRP recommends that documentation for initial and continuing reviews conducted under an expedited review procedure include: (a) the specific permissible categories (see 63 FR 60364-60367 at http://ohrp.osophs.dhhs.gov/humansubjects/guidance/expedited98.htm) justifying the expedited review; and (b) documentation of the review and action taken by the IRB chairperson or designated reviewer and any findings required under the HHS regulations.

(21) Policies for Expedited Review of Minor Changes. OHRP recommends that institutions adopt policies describing the types of minor changes in previously approved research which can be approved by expedited review in accordance with HHS regulations at 45 CFR 46.110(b)(2).

C. REPORTING OF UNANTICIPATED PROBLEMS AND IRB REVIEW OF PROTOCOL CHANGES

Common OHRP Findings of Noncompliance

(22) Failure to Report Unanticipated Problems to IRB, Institutional Officials, and OHRP. OHRP finds that the following unanticipated problems involving risks to subjects or others 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):

(23) 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:}

(24) 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.

Additional OHRP Guidance

(25) Requirement for Review of Proposed Protocol Changes by the IRB at Convened Meetings. 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).

D. APPLICATION OF EXEMPTIONS

Common OHRP Findings of Noncompliance

(26) 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 exempt status to research activities that exceed these categories. OHRP recommends that documentation for all exemptions include citation of the specific category justifying the exemption.

(27) 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.

Additional OHRP Guidance

(28) Procedures for Determining Exemptions. OHRP recommends that institutions adopt clear procedures under which the IRB (or some authority other than the investigator) determines whether proposed research is exempt from the human subjects regulations [see 45 CFR 46.101(b)]. Documentation should include the specific category justifying the exemption.

(29) Applicability 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 DHHS 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.

(30) Applicability 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); (d) The project must not involve significant physical invasions or intrusions upon the privacy of participants (see 12/97 OPRR Guidance @ URL http://ohrp.osophs.dhhs.gov/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. NOTE: Institutions retain the option under their Assurances not to claim the exemptions provided in the regulations, choosing instead to require IRB review of all research involving human intervention/interaction or identifiable private information.

E. INFORMED CONSENT

Common OHRP Findings of Noncompliance

(31) 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.

(32) 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.

(33) 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.

(34) 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 the 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.

(35) 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.

(36) 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.

(37) 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].

(38) Standard Surgical Consent Documents Lack Required Elements of Informed Consent. OHRP notes that standard surgical 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 Section 46.116(d), which requires that the IRB find and document four specific conditions. OHRP finds no documentation of such waiver in protocols for which surgical consent was accepted in lieu of an IRB-approved research consent document.

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

(40) 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.

Additional OHRP Guidance

(41) Informed Consent for Research in Emergency Situations. Nothing in the HHS regulations at 45 CFR Part 46 is intended to limit the authority of a physician to provide emergency medical care, to the extent the physician is permitted to do so under applicable Federal, State, or local law. However, when emergency medical care is initiated without the physician obtaining and documenting the legally effective informed consent of the patient or the patient's legally authorized representative for participation in humans subject research (unless the IRB has appropriately waived such requirements or found that the research is consistent with the Secretary's waiver for emergency research, see OPRR Reports, 97-01 at URL http://ohrp.osophs.dhhs.gov/humansubjects/guidance/hsdc97-01.htm), the patient may not be considered a research subject under 45 CFR Part 46. When emergency care involves investigational drugs, devices, or biologics, U.S. Food and Drug Administration requirements must be satisfied.

(42) Approval and Expiration Dates on Informed Consent Documents. OHRP recommends that IRBs affix the approval and expiration dates to all approved informed consent documents and stipulate that copies of these dated documents must be used in obtaining consent. This procedure helps ensure that only the current, IRB-approved informed consent documents are presented to subjects and serves as a reminder to the investigators of the need for continuing review.

(43) IRB Review of NIH-Approved Informed Consent Documents for NIH-Supported Multicenter Clinical Trials. OHRP requires that each local IRB receive and review a copy of the NIH-approved sample informed consent document and the full NIH-approved protocol as a condition for review and approval of the local informed consent document. Any deletion or substantive modification of information concerning risks or alternative procedures contained in the sample informed consent document must be justified in writing by the investigator, approved by the IRB, and reflected in the IRB minutes (see OPRR Reports 93-01).

(44) Description of Notification of HIV Testing Results. PHS policy (applicable to all PHS-supported intramural and extramural, foreign and domestic research and health activities) requires that where HIV testing is conducted or supported by PHS, individuals whose test results are associated with personal identifiers must be informed of their own test results and provided the opportunity to receive appropriate counseling unless the situation calls for an exception under the special circumstances set forth in the Policy (See OPRR Reports 6/10/88). This procedure should be described in the informed consent document.

(45) Documentation of Informed Consent for Non-English Speakers. The regulations require that informed consent information be presented "in language understandable to the subject" and, in most situations, that informed consent be documented in writing (see 45 CFR 46.116 and 46.117). Where informed consent is documented in accordance with HHS regulations at 45 CFR 46.117(b)(1), the written informed consent document should embody, in language understandable to the subject, all the elements necessary for legally effective informed consent. Subjects who do not speak English should be presented with an informed consent document written in a language understandable to them (see OPRR Guidance November 9, 1995 at URL http://ohrp.osophs.dhhs.gov/humansubjects/guidance/ic-non-e.htm). OHRP strongly encourages the use of this procedure whenever possible.

Alternatively, HHS regulations at 45 CFR 46.117(b)(2) permit oral presentation of informed consent information in conjunction with a short form written informed consent document (stating that the elements of consent have been presented orally) and a written summary of what is presented orally. A witness to the oral presentation is required, and the subject must be given copies of the short form document and the summary. When this procedure is used with subjects who do not speak English, (i) the oral presentation and the short form written informed consent document should be in a language understandable to the subject; (ii) the IRB-approved English language informed consent document may

serve as the summary; and (iii) the witness should be fluent in both English and the language of the subject.

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

Common OHRP Findings of Noncompliance

(46) 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).

(47) 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.

(48) Lack of Prisoner/Prisoner Representative for IRB Review of Research Involving Prisoners. HHS regulations at 45 CFR 46.304 require modification of IRB membership for review of research involving prisoners. In specific, 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.

(49) Conflict Resulting from Office of Research Support (Sponsored Programs) Serving as a Voting Member of the IRB. HHS regulations at 45 CFR 46.107(e) stipulate that no IRB member may participate in the initial or continuing review of any project in which the member has a conflicting interest. The Director of the Office of Research Support (ORS) [**OR** Office of Grants and Contracts] serves as a voting member of the IRB. OHRP suggests that duties of individuals from ORS are likely create a real or apparent conflicting interest and that these individuals ordinarily should not serve as *voting* IRB members.

(50) 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.

(51) Designation of an Additional IRB under an MPA without Prior OHRP Approval. The institution's MPA presently designates [a single] IRB[s]. Designation of additional IRBs under the MPA requires prior notification of and approval by OHRP. OHRP finds that the institution has established an additional IRB without such approval.

(52) 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].

(53) 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.

Additional OHRP Guidance

(54) 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.

For detailed guidance on appropriate mechanisms for ensuring that the IRB has adequate knowledge of the local research context, please see:

http://ohrp.osophs.dhhs.gov/humansubjects/guidance/local.htm

G. DOCUMENTATION OF IRB ACTIVITIES, FINDINGS, AND PROCEDURES

Common OHRP Findings of Noncompliance

(55) 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).

(56) 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.

(57) 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.

(58) 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.

(59) 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.

(60) 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. [**See item (69) below for guidance.**]

(61) 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. [**See item (69) below for guidance.**]

(62) 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. [**See item (69) below for guidance.**]

(63) 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. [**See item (69) below for guidance.**]

(64) 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.

(b) The procedures which the IRB will follow for conducting its continuing review of research.

(c) The procedures which the IRB will follow for reporting its findings and actions to investigators and the institution.

(d) The procedures which the IRB will follow for determining which projects require review more often than annually.

(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.

(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.

(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.

(65) 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 OPRR guidance regarding repositories, 11/97 at URL http://ohrp.osophs.dhhs.gov/humansubjects/guidance/reposit.htm).

(66) 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.

Additional OHRP Guidance

(67) 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.

(68) Recording of Votes in IRB Minutes. HHS regulations at 45 CFR 46.115(a)(2) require that the minutes of IRB meetings document the vote on all IRB actions including the number of members voting for, against, and abstaining. In order to document the continued existence of a quorum, OHRP recommends that votes be recorded in the minutes using the following format: Total = 15; Vote: For-14, Opposed-0, Abstained-1 (NAME).

(69) Documentation of Required IRB Findings in IRB Minutes. HHS regulations at 45 CFR 46.116(d) require that the IRB make and document four findings when approving a consent procedure which does not include, or which alters, some or all of the required elements of informed consent or when waiving the requirement to obtain informed consent. OHRP recommends that when approving such a waiver for research reviewed by the convened IRB, these findings be documented in the minutes of the IRB meeting, including *protocol-specific* information justifying each IRB finding.

Similarly, where HHS regulations require specific findings on the part of the IRB, such as (a) approving a procedure which waives the requirement for obtaining a signed consent form [see 45 CFR 46.117(c)]; (b) approving research involving pregnant women, human fetuses, or neonates (see 45 CFR 46.204-207); (c) approving research involving prisoners (see 45 CFR 46.305-306); or (d) approving research involving children (see 45 CFR 46.404-407), the IRB should document such findings. OHRP recommends that for research approved by the convened IRB, all required findings be fully documented in the minutes of the IRB meeting, including *protocol-specific* information justifying each IRB finding.

For research reviewed under an expedited review procedure, these findings should be documented by the IRB Chairperson or other designated reviewer elsewhere in the IRB record.

(70) Documentation of Risk and Approval Period in IRB Minutes. IRBs must determine which protocols require continuing review more often than annually, as appropriate to the degree of risk [see 45 CFR 46.103(b)(4) and 46.109(e)]. OHRP recommends that the minutes of IRB meetings clearly reflect these determinations regarding risk and approval period (review interval).

(71) IRB Policies and Procedures– Operational Details. Written IRB policies and procedures should provide a step-by-step description with key operational details for each of the procedures required by HHS regulations at 45 CFR 46.103(b)(4) and (5):

> (a) A description of any primary reviewer system used for initial review, continuing review, review of protocol changes, and/or review of reports of unanticipated problems involving risks to subjects or others or of serious or continuing noncompliance.
>
> (b) Lists of specific documents distributed to primary reviewers (if applicable) and to all other IRB members for initial review, continuing review, review of protocol changes, and review of reports of unanticipated problems involving risks to subjects or others or of serious or continuing noncompliance.

(c) Details of any process (e.g., a subcommittee procedure) that may be used to supplement the IRB's initial review, continuing review, review of protocol changes, and/or review of reports of unanticipated problems involving risks to subjects or others or of serious or continuing noncompliance.

(d) The timing of document distribution prior to IRB meetings.

(e) The range of possible actions taken by the IRB for protocols undergoing initial or continuing review and protocol changes undergoing review.

(f) A description of how expedited review is conducted and how expedited approval actions are communicated to all IRB members.

(g) A description of the procedures for: (i) communicating to investigators IRB action regarding proposed research and any modifications or clarifications required by the IRB as a condition for IRB approval of proposed research; and (ii) reviewing and acting upon investigators' responses.

(h) A description of which institutional office(s) and official(s) are notified of IRB findings and actions and how notification to each is accomplished.

(i) A description, if applicable, of which institutional office(s) or official(s) is responsible for further review and approval or disapproval of research that is approved by the IRB. Please note that, in accordance with HHS regulations at 45 CFR 46.112, no other institutional office or official may approve research that has not been approved by the IRB.

(j) A specific procedure for how the IRB determines which protocols require review more often than annually, including specific criteria used to make these determinations (e.g., an IRB may set a shorter approval period for high-risk protocols or protocols with a high risk:potential benefit ratio).

(k) A specific procedure for how the IRB determines which projects need verification from sources other than the investigators that no material changes have occurred since previous IRB review, including specific criteria used to make these determinations (e.g., such criteria could include some or all of the following: (i) randomly selected projects; (ii) complex projects involving unusual levels or types of risk to subjects; (iii) projects conducted by investigators who previously have failed to comply with the requirements of the HHS regulations or the requirements or determinations of the IRB; and (iv) projects where concern about possible material changes occurring without IRB approval have been raised based upon information provided in continuing review reports or from other sources).

(l) A description of what steps are taken to ensure that investigators do not implement any protocol changes without prior IRB review and approval, except when necessary to eliminate apparent immediate hazards to subjects (e.g., this might be addressed through training programs and materials for investigators, specific directives included in approval letters to investigators, and random audits of research records).

(m) A description of which office(s) or institutional official(s) is responsible for promptly reporting to the IRB, appropriate institutional officials, any supporting Agency or Department heads, and OHRP any (i) unanticipated problems involving risks to subjects or others; (ii) any serious or continuing noncompliance with 45 CFR Part 46 or the requirements or determinations of the IRB; and (iii) any suspension or termination of IRB approval.

(n) A description of the required time frame for accomplishing the reporting requirements in the preceding paragraph.

(o) The range of possible actions taken by the IRB in response to reports of unanticipated problems involving risks to subjects or others or of serious or continuing noncompliance.

(p) Institutions may wish to consider including additional pertinent information in their written IRB procedures, such as the following: (a) important definitions (e.g., the definition of *research, human subject*, and *minimal risk)*; (b) a description of procedures for implementing other relevant Federal regulations that apply to human subject research (e.g., FDA and HIPAA regulations); (c) procedures for selecting and appointing the IRB chairperson and members in order to satisfy the requirements of HHS regulations at 45 CFR 46.107; (d) procedures for training and educating IRB members and staff and investigators; (e) a description of the required elements of informed consent and criteria for waiving or altering these requirements; and (f) procedures for ensuring that the IRB possesses sufficient knowledge of the local research context.

(72) Handbook of IRB Guidelines and Procedures for Investigators. OHRP strongly recommends that institutions develop and distribute a handbook of IRB guidelines for research investigators. The handbook should include detailed information concerning (a) federal and institutional requirements for the protection of human research subjects; (b) the IRB's role and responsibilities; (c) the requirements and procedures for initial and continuing IRB review and approval of research; (d) the rationale and procedures for proposing that the research may meet the criteria for expedited review; (e) the requirements and procedures for verifying that research is exempt from IRB review; (f) the responsibilities of investigators during the review and conduct of research; (g) the requirements and procedures for notifying the IRB of unanticipated problems or events involving risks to the subjects, as well as any other expected or unexpected adverse events; (h) an explanation of the distinction between FDA requirements for emergency use of test articles versus HHS regulations for the conduct of human subjects research; (i) relevant examples and user-friendly forms for providing information to the IRB;

and (j) a copy of the institution's MPA, the HHS humans subjects regulations (45 CFR Part 46), and *The Belmont Report*. Where appropriate, OHRP also recommends that IRBs develop written operating procedures to supplement its guidelines for investigators.

H. MISCELLANEOUS OHRP GUIDANCE

(73) Protocol Revisions - Incorporation Into Written Protocol. OHRP recommends that each revision to a research protocol be incorporated into the written protocol. This practice ensures that there is only one complete protocol with the revision dates noted on each revised page and the first page of the protocol itself. This procedure is consistent with the procedure used for revised and approved informed consent documents which then supersede the previous one.

(74) Operation of Student "Human Subject Pools". OHRP recommends that IRBs exercise oversight over the operation of student "human subject pools." Subject pool procedures must be in accordance with HHS regulations and must ensure (a) that consent for participation is sought only under circumstances which minimize the possibility of coercion or undue influence, and (b) that genuinely equivalent alternatives to participation are available.

(75) Procedures for Control of Investigational Agents. OHRP recommends that institutions develop procedures to ensure appropriate control of investigational agents through (a) control of such agents through a central pharmacy; (b) written notification to the pharmacy by the IRB when protocols are approved, suspended, or terminated; and (c) verification of informed consent by the pharmacy before dispensing to subjects.

(76) Applicability of State and Local Laws to HHS-Supported Research. The HHS regulations do not affect any applicable State or local laws or regulations which provide additional protections for human subjects [see 45 CFR 46.101(f)]. OHRP recommends that written IRB procedures describe applicable State and local laws and regulations relevant to the conduct of human subject research.

(77) Fetal Tissue Transplantation Research. Sections 498 and 498A of the Public Health Service Act (42 USC 289g and 289g-1) establish specific conditions for conduct of HHS-supported research on transplantation of human fetal tissue for therapeutic purposes. Among these conditions are special requirements for informed consent of the donor, informed consent of the researcher and donee, availability of statements for audit, and reporting to Congress.