NOTE: THIS GUIDANCE REPLACES OHRP'S JULY 11, 2002 GUIDANCE ENTITLED "GUIDANCE ON WRITTEN IRB PROCEDURES." CLICK HERE FOR THE JULY 11, 2002 GUIDANCE. THIS GUIDANCE HAS BEEN UPDATED TO INCLUDE THE FOLLOWING CHANGES: (1) CONTENT REGARDING CONTINUING REVIEW HAS BEEN REVISED TO BE CONSISTENT WITH THE CONTENT OF OHRP'S JANUARY 15, 2007 "GUIDANCE ON REVIEWING AND REPORTING UNANTICIPATED PROBLEMS INVOLVING RISKS TO SUBJECTS OR OTHERS AND ADVERSE EVENTS;" (2) PARAGRAPH A.(4) UNDER "ADDITIONAL OHRP GUIDANCE RELEVANT TO WRITTEN IRB PROCEDURES" HAS BEEN REVISED TO BE CONSISTENT WITH OHRP'S POSITION REGARDING WHEN IRB'S MUST DEFER APPROVAL OF RESEARCH; AND (3) FORMATTING CHANGES.

Office for Human Research Protections (OHRP)
Department of Health and Human Services

This guidance represents OHRP's current thinking on this topic and should be viewed as recommendations unless specific regulatory requirements are cited. The use of the word *must* in OHRP guidance means that something is required under HHS regulations at 45 CFR part 46. The use of the word *should* in OHRP guidance means that something is recommended or suggested, but not required. An institution may use an alternative approach if the approach satisfies the requirements of the HHS regulations at 45 CFR part 46. OHRP is available to discuss alternative approaches at 240-453-6900 or 866-447-4777.

Guidance on Written IRB Procedures

Date: January 15, 2007

Scope: This document outlines the required elements of written Institutional Review Board (IRB) procedures under Department of Health and Human Services (HHS) regulations for the protection of human subjects (45 CFR Part 46) and provides an overview of relevant OHRP guidance regarding each required element.

Target Audience: This document primarily is intended to assist IRB administrators, IRB chairpersons, and other relevant institutional officials who may be responsible for preparing and maintaining written IRB procedures.

BACKGROUND

OHRP frequently receives requests for guidance and clarification regarding the content of written IRB procedures. In order to assist institutions in developing adequate written IRB procedures, OHRP has compiled the following summary of the relevant regulatory requirements

and guidance issued routinely by OHRP over the past several years.
OHRP has not developed a model written IRB procedures document for institutions to adapt because procedures appropriately can vary significantly among institutions as the result of differences in institution size, the type of research activities, institutional administrative practices, number of IRBs, and local and state laws and regulations. For each required element, the written IRB procedures should provide sufficient step-by-step operational details so that an independent observer can understand how an IRB operates and conducts its major functions.

REGULATORY REQUIREMENTS

HHS regulations at 45 CFR 46.103(b)(4) and (5) require that institutions have written IRB procedures for each of the following:

(1) the procedures which the IRB will follow for conducting its initial review of research;

(2) the procedures which the IRB will follow for conducting its continuing review of research;

(3) the procedures which the IRB will follow for reporting its findings and actions to investigators and the institution;

(4) the procedures which the IRB will follow for determining which projects require review more often than annually;

(5) 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;

(6) 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; and

(7) 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 (hereinafter referred to as *unanticipated problems*);
(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.

GUIDANCE ON OPERATIONAL DETAILS

Written IRB procedures should provide a step-by-step description with key operational details for each of the above procedures. Important operational details for the above procedures should include:

(1) 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 or of serious or continuing noncompliance;

(2) 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 or of serious or continuing noncompliance;

(3) 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 or of serious or continuing noncompliance;

(4) the timing of document distribution prior to IRB meetings;

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

(6) a description of how expedited review is conducted and how expedited approval actions are communicated to all IRB members;

(7) a description of the procedures for:

(a) 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
(b) reviewing and acting upon investigators' responses;

(8) a description of which institutional office(s) and official(s) are notified of IRB findings and actions and how notification to each is accomplished;

(9) 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;

(10) 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);

(11) 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:

(a) randomly selected projects;
(b) complex projects involving unusual levels or types of risk to subjects;
(c) 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
(d) 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);

(12) 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);

(13) 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:
(a) unanticipated problems;
(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;

(14) a description of the required time frame for accomplishing the reporting requirements in the preceding paragraph; and

(15) the range of possible actions taken by the IRB in response to reports of unanticipated problems or of serious or continuing noncompliance.

ADDITIONAL OHRP GUIDANCE RELEVANT TO WRITTEN IRB PROCEDURES

A. Guidance Relevant to Initial and Continuing Review

(1) **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://www.hhs.gov/ohrp/humansubjects/guidance/63fr60364.htm). Approval of research is by a majority vote of this quorum. 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.

(2) **Research Review Materials**

(a) **Initial Review Materials.** 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. 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.

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.

(b) **Continuing Review Materials.** Continuing review of research must be substantive and meaningful. The IRB must ensure that the criteria set forth by HHS regulations at 45 CFR 46.111 are satisfied at the time of 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 that includes:

- the number of subjects accrued;
- a summary of any unanticipated problems and available information regarding adverse events (in many cases, such a summary could be a simple brief statement that there have been no unanticipated problems and that adverse events have occurred at the expected frequency and level of severity as documented in the research protocol, the informed consent document, and any investigator brochure);
- a summary of any withdrawal of subjects from the research since the last IRB review;
- a summary of any complaints about the research since the last IRB review;
- a summary of any recent literature that may be relevant to the research and any amendments or modifications to the research since the last IRB review;
- any relevant multi-center trial reports;
- any other relevant information, especially information about risks associated with the research; and
- 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 members 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.

For additional details about OHRP's guidance on continuing review, see http://www.hhs.gov/ohrp/humansubjects/guidance/contrev0107.htm.

(3) **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://www.hhs.gov/ohrp/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.

(4) **Contingent Approval of Research.** Convened IRBs often set conditions under which a protocol can be approved. OHRP notes that when the convened IRB requests substantive clarifications or modifications regarding the protocol or informed consent process/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.

(5) **Conflicting Interest.** 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 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.

(6) **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://www.hhs.gov/ohrp/humansubjects/guidance/63fr60364.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.

B. Guidance Relevant to IRB Records and Documentation

(1) **IRB Protocol Records.** IRB protocol records must include all the information stipulated by HHS regulations at 45 CFR 46.115(a)(1), (3), (4), and (7).

(2) **Minutes of IRB Meetings**. The minutes of IRB meetings must include all the information stipulated by HHS regulations at 45 CFR 46.115(a)(2). The minutes of IRB meetings should document, among other things:

(a) Separate deliberations, actions, and votes for each protocol undergoing initial or continuing review by the convened IRB.

(b) 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.

(3) **Documentation of Findings.** 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.

(4) **Documentation of Risk and Approval Period.** 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).

(5) **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.

C. Guidance Relevant to Review of Protocol Changes

(1) **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).

(2) **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 under an expedited review procedure in accordance with HHS regulations at 45 CFR 46.110(b)(2).

(3) **Protocol Revisions.** 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.

D. Miscellaneous Guidance

(1) **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.

(2) **Informed Consent Documents: Approval and Expiration Dates.** 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.

(3) **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.

(4) **Additional Considerations.** 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.