

NOTE: THIS GUIDANCE REPLACES OHRP'S JULY 11, 2002 GUIDANCE ENTITLED "GUIDANCE ON CONTINUING REVIEW." [CLICK HERE](#) FOR THE JULY 11, 2002 GUIDANCE. THIS GUIDANCE HAS BEEN UPDATED 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."

**Office for Human Research Protections
Department of Health and Human Services**

Guidance on Continuing Review

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.

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Scope: This document describes the requirements of Department of Health and Human Services (HHS) regulations at 45 CFR 46.109(e) for the continuing review of human subjects research by an Institutional Review Board (IRB) at intervals appropriate to the degree of risk, but not less than once per year. In particular, OHRP offers guidance on the following topics:

1. [what constitutes substantive and meaningful continuing review](#);
2. [what are some additional considerations for continuing review of multi-center trials monitored by a Data and Safety Monitoring Board \(DSMB\), Data Monitoring Committee \(DMC\), other similar body, or sponsor](#);
3. [when may expedited review procedures be used for continuing review](#);
4. [how is the continuing review date determined](#);
5. [what occurs if there is a lapse in continuing review](#); and
6. [what is the required composition of IRBs specifically designated to conduct continuing review](#).

Target Audience: IRBs, investigators, research institutions, and sponsors.

REGULATORY REQUIREMENTS

The HHS regulations for the protection of human subjects (45 CFR Part 46) require that, among other things, (1) institutions have written procedures which the IRB will follow for (a) conducting its continuing review of research and for reporting its findings and actions to investigators and the institution, and (b) determining which projects require review more often than annually (45 CFR 46.103(b)(4)); (2) except when an expedited review procedure is used, each IRB reviews proposed research 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 the nonscientific areas (45 CFR 46.108(b)); and (3) an IRB conducts continuing review of research at intervals appropriate to the degree of risk, but not less often than once a year (45 CFR 46.109(e)).

WHAT CONSTITUTES SUBSTANTIVE AND MEANINGFUL CONTINUING REVIEW?

Continuing review of research must be substantive and meaningful. In accordance with HHS regulations at 45 CFR 46.108(b) and at 46.115(a)(2), continuing review by the convened IRB, with recorded vote on each study, is required unless the research is otherwise appropriate for expedited review under Section 46.110 (see below). Furthermore, 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. In particular, when conducting continuing review, the IRB needs to determine whether any new information has emerged – either from the research itself or from other sources – that could alter the IRB’s previous determinations, particularly with respect to risk to subjects. Of note, information regarding any unanticipated problems involving risks to subjects or others (hereinafter referred to as unanticipated problems) that have occurred since the previous IRB review in most cases will be pertinent to the IRB’s determinations 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 member also should have access to the complete IRB protocol file and relevant IRB minutes prior to or during the convened IRB meeting.

When reviewing the current informed consent document(s), the IRB should ensure the following:

- The currently approved or proposed consent document is still accurate and complete;
- Any significant new findings that may relate to the subject's willingness to continue participation are provided to the subject in accordance with HHS regulations at 45 CFR 46.116(b)(5).

Review of currently approved or newly proposed consent documents must occur during the scheduled continuing review of research by the IRB, but informed consent documents should be reviewed whenever new information becomes available that would require modification of information in the informed consent document.

Furthermore, 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.

WHAT ARE SOME ADDITIONAL CONSIDERATIONS FOR CONTINUING REVIEW OF MULTI-CENTER TRIALS MONITORED BY A DSMB, DMC, OTHER SIMILAR BODY, OR SPONSOR?

As noted above, continuing review of research by the IRB should include consideration of, among other things, unanticipated problems, adverse events, and any recent literature that may be relevant to the research.

OHRP recognizes that local investigators participating in multicenter clinical trials usually are unable to prepare a meaningful summary of adverse events for their IRBs because study-wide information regarding adverse events is not readily available to them. In such circumstances, when the clinical trial is subject to oversight by a monitoring entity (e.g., the research sponsor, a

coordinating or statistical center, or a DSMB/DMC), OHRP recommends that at the time of continuing review local investigators submit to their IRBs a current report from the monitoring entity. OHRP further recommends that such reports include the following:

- (1) a statement indicating what information (e.g., study-wide adverse events, interim findings, and any recent literature that may be relevant to the research) was reviewed by the monitoring entity;
- (2) the date of the review; and
- (3) the monitoring entity's assessment of the information reviewed.

It may also be appropriate for the IRB at the time of continuing review to confirm that any provisions under the previously approved protocol for monitoring study data to ensure safety of subjects have been implemented and are working as intended (e.g., the IRB could require that the investigator provide a report from the monitoring entity described in the IRB-approved protocol).

WHEN MAY EXPEDITED REVIEW PROCEDURES BE USED FOR CONTINUING REVIEW?

The HHS human subjects 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.hhs.gov/ohrp/humansubjects/guidance/63fr60364.htm>), and to the review of minor changes in previously approved research during the period (of one year or less) for which approval is authorized. IRBs are permitted to use expedited review for the continuing review of research that involves solely one or more of the activities published at 63 FR 60364-60367.

Generally, if research did not qualify for expedited review at the time of initial review, it does not qualify for expedited review at the time of continuing review, except in limited circumstances described by expedited review categories (8) and (9) at 63 FR 60364-60367. It is also possible that research activities that previously qualified for expedited review in accordance with HHS regulations at 45 CFR 46.110, have changed or will change, such that expedited IRB review would no longer be permitted for continuing review.

Expedited Review Category (8):

Under Category (8), an expedited review procedure may be used for the continuing review of research previously approved by the convened IRB as follows:

- (a) Where (i) the research is permanently closed to the enrollment of new subjects; (ii) all subjects have completed all research-related interventions; and (iii) the research remains active only for long-term follow-up of subjects; **OR**

- (b) Where no subjects have been enrolled and no additional risks have been identified;
OR
- (c) Where the remaining research activities are limited to data analysis.

Of note, category (8) identifies three situations in which research that is greater than minimal risk and has been initially reviewed by a convened IRB may undergo subsequent continuing review by the expedited review procedure.

For a multi-center protocol, an expedited review procedure may be used by the IRB at a particular site whenever the conditions of category (8)(a), (b), or (c) are satisfied for that site. However, with respect to category 8(b), while the criterion that "no subjects have been enrolled" is interpreted to mean that no subjects have ever been enrolled at a particular site, the criterion that "no additional risks have been identified" is interpreted to mean that neither the investigator nor the IRB at a particular site has identified any additional risks from any site or other relevant source.

Expedited Review Category (9):

Under Category (9), an expedited review procedure may be used for continuing review of research not conducted under an investigational new drug application or investigational device exemption where categories (2) through (8) do not apply but the IRB has determined and documented at a convened meeting that the research involves no greater than minimal risk and no additional risks have been identified.

The determination that "no additional risks have been identified" does not need to be made by the convened IRB.

HOW IS THE CONTINUING REVIEW DATE DETERMINED?

HHS regulations at 45 CFR 46.108(b) and 109(e) require, respectively, that (1) except when an expedited review procedure is used, each IRB must review proposed research 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; and (2) an IRB must conduct continuing review of research at intervals appropriate to the degree of risk, but not less frequently than once per year. The IRB should decide the frequency of continuing review for each study protocol necessary to ensure the continued protection of the rights and welfare of research subjects.

Several scenarios for determining the date of continuing review apply for protocols reviewed by the IRB at a convened meeting. To determine the date by which continuing review must occur, focus on the date of the convened meeting at which IRB approval occurs. (These examples presume the IRB has determined that it will conduct continuing review no sooner than within 1 year).

Scenario 1: The IRB reviews and approves a protocol without any conditions at a convened meeting on October 1, 2002. Continuing review must occur within 1 year of the date of the meeting, that is, by October 1, 2003.

Scenario 2: The IRB reviews a protocol at a convened meeting on October 1, 2002, and approves the protocol contingent on specific minor conditions the IRB chair or his/her designee can verify. On October 31, 2002, the IRB chair or designee confirms that the required minor changes were made. Continuing review must occur within 1 year of the date of the convened IRB meeting at which the IRB reviewed and approved the protocol, that is, by October 1, 2003.

Scenario 3: The IRB reviews a study at a convened meeting on October 1, 2002, and has serious concerns or lacks significant information that requires IRB review of the study at subsequent convened meetings on October 15 and October 29, 2002. At their October 29, 2002 meeting, the IRB completes its review and approves the study. Continuing review must occur within 1 year of the date of the convened meeting at which the IRB reviewed and approved the protocol, that is, by October 29, 2003.

Expedited Review

For a study approved under expedited review, continuing review must occur within 1 year of the date the IRB Chair or IRB member(s) designated by the Chair gives final approval to the protocol.

Review of a change in a protocol ordinarily does not alter the date by which continuing review must occur. This is because continuing review is review of the full protocol, not simply a change to it.

The regulations make no provision for any grace period extending the conduct of research beyond the expiration date of IRB approval. Therefore, continuing review and re-approval of research must occur on or before the date when IRB approval expires. OHRP recognizes the logistical advantages of keeping the IRB approval period constant from year to year throughout the life of each project. When continuing review occurs annually and the IRB performs continuing review within 30 days before the IRB approval period expires, the IRB may retain the anniversary date as the date by which the continuing review must occur. This would be, for example, October 1, 2003, in the above Scenarios 1 and 2, and October 29, 2003, in Scenario 3, even if the continuing reviews took place up to 30 days prior to these dates.

WHAT OCCURS IF THERE IS A LAPSE IN CONTINUING REVIEW?

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.

When continuing review of a research protocol does not occur prior to the end of the approval period specified by the IRB, IRB approval expires automatically. Such expiration of IRB approval does not need to be reported to OHRP as a suspension of IRB approval under HHS regulations.

WHAT IS THE REQUIRED COMPOSITION OF IRBS SPECIFICALLY DESIGNATED TO CONDUCT CONTINUING REVIEW?

OHRP is aware that some institutions have designated one or more IRBs for the sole purpose of conducting continuing review. While OHRP acknowledges that such a practice is permissible under the HHS regulations for the protection of human subjects, OHRP reminds institutions that such IRBs must comply with the IRB membership requirements stipulated by HHS regulations at 45 CFR 46.107. In particular, HHS regulations at 45 CFR 46.107(a) require the following for all IRBs, including IRBs that are solely responsible for continuing review:

The IRB must have at least five members with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the institution. The IRB must be sufficiently qualified through the experience and expertise of its members, and the diversity of 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 in safeguarding the rights and welfare of human subjects. In addition to possessing the professional competence necessary to review specific research activities, the IRB shall be able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice. The IRB must therefore include persons knowledgeable in these areas. If the IRB regularly reviews research that involves a vulnerable category of subjects, such as children, prisoners, pregnant women, or handicapped or mentally disabled persons, consideration shall be given to the inclusion of one or more individuals who are knowledgeable about and experienced in working with these subjects.

In addition, it should be noted that the other requirements for IRB membership at 45 CFR 46.107(b)-(f) also apply to IRBs conducting continuing review.

OTHER PERTINENT REGULATIONS

For FDA-regulated research, see 21 CFR 50, and 21 CFR 56.