

Guidance on IRB Continuing Review of Research

This draft guidance, when finalized, will represent the Office for Human Research Protections' (OHRP's) current thinking on this topic and will supersede OHRP's [January 15, 2007 Guidance on Continuing Review](#). OHRP guidance 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 the Department of Health and Human Services (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 45 CFR part 46. OHRP is available to discuss alternative approaches by telephone at 240-453-8237 or 866-447-4777, or by email at ohrp@hhs.gov.

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Scope: This guidance document, when finalized, will apply to research involving human subjects that is conducted or supported by HHS. It provides guidance on the HHS regulations for the protection of human research subjects at 45 CFR part 46 related to institutional review board (IRB) continuing review of research. In particular, the guidance addresses the following topics:

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Target Audience: IRBs, investigators, HHS funding agencies, and others that may be responsible for the review, conduct, or oversight of human subjects research conducted or supported by HHS.

Regulatory Background:

The HHS regulations for the protection of human subjects at 45 CFR part 46 have several provisions pertinent to continuing review of research, including the following:

- An institution (or when appropriate an IRB) must prepare and maintain – and the IRB must follow – written procedures for:
 - Conducting continuing review of research and for reporting its findings and actions to the investigator and the institution;

- Determining which projects require review more often than annually and which projects need verification from sources other than the investigators that no material changes in the research have occurred since the previous IRB review; and
 - Ensuring prompt reporting to the IRB of proposed changes in a research activity and for ensuring that 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 human subjects (45 CFR 46.103(b)(4), 46.108(a), and 46.115(a)(6)).
- No IRB may have a member participate in the IRB's continuing review of any project in which the member has a conflicting interest, except to provide information requested by the IRB (45 CFR 46.107(e)).
 - Except when an expedited review procedure is used, continuing review of research must occur at convened meetings at which a majority of the IRB members are present, including at least one member whose primary concerns are in nonscientific areas. In order for research undergoing continuing review to be approved, it must receive the approval of a majority of those members present at the meeting. (45 CFR 46.108(b)).
 - *IRB approval* means the determination of the IRB that the research has been reviewed and may be conducted at an institution within the constraints set forth by the IRB and by other institutional and federal requirements (45 CFR 46.102(h)).
 - An IRB must conduct continuing review of research at intervals appropriate to the degree of risk, but not less than once per year (45 CFR 46.109(e)).
 - An IRB may use an expedited review procedure to conduct continuing review of research for some or all of the research appearing on the list of research eligible for expedited review (see <http://www.hhs.gov/ohrp/humansubjects/guidance/expedited98.htm>) and found by the reviewer(s) to involve no more than minimal risk. Under an expedited review procedure, the review may be carried out by the IRB chairperson or by one or more experienced reviewers designated by the IRB chairperson from among the members of the IRB. In reviewing the research, the reviewers may exercise all of the authorities of the IRB except that the reviewers may not disapprove the research. For any research approved under an expedited review procedure at the time of continuing review, all members must be advised of such approvals. OHRP may restrict, suspend, terminate, or choose not to authorize an IRB's use of the expedited review procedure. (45 CFR 46.110)
 - In order to approve research, the IRB must determine that all of the requirements of 45 CFR 46.111 are satisfied. In addition, for research involving pregnant women, fetuses or neonates; prisoners; or children, the IRB must determine that the research satisfies the requirements of subpart B, C, or D, respectively, of 45 CFR part 46.
 - An institution, or when appropriate an IRB, must prepare and maintain adequate documentation of IRB activities, including the following:

- Copies of all research proposals reviewed, scientific evaluations, if any, that accompany the proposals, approved sample consent documents, progress reports submitted by investigators, and reports of injuries to subjects;
- Minutes of IRB meetings which shall 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 any controverted issues and their resolution;
- Records of continuing review activities;
- Copies of all correspondence between the IRB and the investigators;
- Written procedures for the IRB in the same detail as required in 45 CFR 46.103(b)(4) and (5); and
- Statements of significant new findings provided to subjects, as required by 45 CFR 46.116(b)(5) (45 CFR 46.115(a)).

Guidance:

A. Introduction

This guidance is intended to assist IRBs in carrying out their continuing review responsibilities under 45 CFR part 46 by providing recommendations regarding, among other things, the approval criteria, process, and frequency for continuing review to assure the protection of the rights and welfare of human subjects participating in research. The guidance also is intended to help investigators and others involved in the review, conduct, or oversight of research better understand their responsibilities related to continuing review.

An institution (or when appropriate an IRB) must prepare and maintain written procedures for conducting continuing review (45 CFR 46.103(b)(4)). The purpose of these written procedures is to ensure that IRBs have a framework for periodically reviewing the conduct of research by investigators. While a research project is ongoing, the IRB reviews and considers proposed changes to the research as they are received, including protocol and consent form amendments. They also periodically receive and review reports of unanticipated problems involving risks to subjects or others (hereinafter referred to as “unanticipated problems”) and other information about the research. Although an IRB may become familiar with various individual aspects of the research project’s conduct, such familiarity does not relieve the IRB of the responsibility to conduct continuing review at least annually, which provides an opportunity to reassess the totality of the project and assure that, among other things, risks to subjects are being minimized and are still reasonable in relation to anticipated benefits, if any, to the subjects and the knowledge that is expected to result.

B. Key IRB Considerations When Evaluating Research Undergoing Continuing Review

1. Criteria for IRB Approval of Research Undergoing Continuing Review

HHS regulations set forth the criteria for IRB approval of research (45 CFR 46.111, 46.204-207, 46.305, and 46.404-409). These criteria apply to both initial review and continuing review of research and provide the framework for the IRB's evaluation of research. In order to re-approve research at the time of continuing review, the IRB must determine that all of following requirements are satisfied:

- Risks to subjects are minimized (i) by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes (45 CFR 46.111(a)(1));
- Risks to subjects are reasonable in relation to anticipated benefits, if any, to the subjects and the importance of the knowledge that may reasonably be expected to result (45 CFR 46.111(a)(2));
- Selection of subjects is equitable (45 CFR 46.111(a)(3));
- Informed consent will be sought from each prospective subject or the subject's legally authorized representative, and appropriately documented in accordance with, and to the extent required by, HHS regulations at 45 CFR 46.116 and 46.117, respectively (45 CFR 46.111(a)(4) and (5));
- When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects (45 CFR 46.111(a)(6));
- When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data (45 CFR 46.111(a)(7));
- Appropriate safeguards are included to protect subjects likely to be vulnerable to coercion or undue influence (45 CFR 46.111(b)); and
- When the research involves pregnant women, fetuses, or neonates; prisoners; or children, the research satisfies the additional requirements for IRB approval under HHS regulations at subpart B, C, or D, respectively, of 45 CFR part 46.

When conducting continuing review, the IRB should start with the working presumption that the research, as previously approved, does satisfy all of the above criteria. The IRB should focus on whether there is any new information provided by the investigator¹, or otherwise available to the IRB, that would alter the IRB's prior determinations, particularly with respect to the IRB's prior evaluation of the potential benefits or risks to the subjects. The IRB also should assess whether there is any new information that would necessitate revision of the protocol and/or the informed consent document. IRBs have the authority to disapprove or require modifications in (to secure re-approval of) a research activity that does not meet the above criteria (45 CFR 46.109(a)). If research does not satisfy all of the above criteria, the IRB must require changes that would result in research satisfying these criteria, defer taking action, or disapprove the research.

¹ For the sake of simplification, in this sentence and many subsequent sentences, OHRP has used the singular noun "investigator" when the plural noun "investigators" may also be appropriate.

When conducting continuing review and evaluating whether research continues to satisfy the criteria for IRB approval of research, IRBs should pay particular attention to the following four aspects of the research:

- Risk assessment and monitoring;
- Adequacy of the process for obtaining informed consent;
- Investigator and institutional issues; and
- Research progress.

2. Risk Assessment and Monitoring

One of the most important considerations for the IRB at the time of continuing review is whether there is any new information provided by the investigator, or otherwise available to the IRB, that would alter the IRB's previous conclusion that (1) the risks to subjects are minimized, and (2) the risks to subjects are reasonable in relation to anticipated benefits, if any, to the subjects and the importance of the knowledge that may reasonably be expected to result (45 CFR 46.111(a)(1) and (2)). The IRB's continuing review procedures should ensure that the IRB will consider relevant information received since the date of the last IRB review and approval of the research project from the investigator, any monitoring entity (e.g., the research sponsor, a coordinating or statistical center, an independent medical monitor, a data and safety monitoring board (DSMB), or a data monitoring committee (DMC)), or any other source. Information regarding any unanticipated problems and adverse events that have occurred since the previous IRB review in particular will be pertinent to the IRB's determinations at the time of continuing review regarding the risk:benefit relationship of the research (see OHRP's *Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events* at <http://www.hhs.gov/ohrp/policy/AdvEvtGuid.htm>).

It also may be appropriate for the IRB at the time of continuing review to confirm that any provisions under the previously approved protocol for monitoring the research data to ensure safety of subjects (45 CFR 46.111(a)(6)) 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).

3. Evaluating the Adequacy of the Informed Consent Process

At the time of continuing review, the IRB should review the informed consent document to verify that the investigator is using the most recently approved version and that the document contains the most accurate, up-to-date information about the research. OHRP recommends that IRBs consider using methods that will allow the IRB to readily recognize the most current version of the IRB-approved informed consent document, for example, using date stamps or initialing and dating documents to indicate when a version was approved.

Likewise, if the IRB waived the requirement for the investigator to obtain a signed consent form for some or all subjects (45 CFR 46.117(c)), the IRB should assess the accuracy of the content of

the information being provided to subjects orally and of any written statement regarding the research that is being provided to subjects.

When reviewing an informed consent document, the IRB must ensure that the currently approved or proposed consent document adequately addresses the elements of informed consent required under 45 CFR 46.116(a) and (b). The IRB should be particularly attentive to whether the informed consent document provides an accurate and up-to-date description of the reasonably foreseeable risks and discomforts of the research to the subjects (45 CFR 46.116(a)(2)) and any appropriate alternative procedures or courses of treatment that might be advantageous to the subject (45 CFR 46.116(a)(4)).

The IRB also should assess whether there is any new information presented by the investigator or others (for example, subjects or other individuals who have observed the investigator obtaining subjects' informed consent) that raises concerns about the circumstances under which informed consent is being obtained. For example, the IRB should assess whether there is any new information indicating that the investigator may not be obtaining informed consent under circumstances that provide subjects with sufficient opportunity to consider whether or not to participate or that minimize the possibility of coercion or undue influence (see 45 CFR 46.116).

As part of the process for obtaining informed consent, subjects must be provided, when appropriate, with a statement that significant new findings developed during the course of the research which may relate to the subjects' willingness to continue participation will be provided to the subjects (45 CFR 46.116(b)(5)). Continuing review provides the IRB with an opportunity to determine whether there is any new information that should be considered to represent such a significant new finding and therefore be communicated to subjects who have already enrolled in the research (e.g., important new toxicity information or new adverse event information related to the research interventions that is identified during analysis of the research data).

4. Evaluating Investigator and Institutional Issues

When appropriate, the reviewing IRB should consider issues regarding the investigator and the institution(s) where the research is being conducted during its continuing review, such as the following:

- Changes in the investigator's situation or qualifications (e.g., suspension of hospital privileges, change in medical license status, or increase in number of research studies conducted by the investigator);
- Evaluation, investigation, and resolution of any complaints related to the investigator's conduct of the research;
- Changes in the acceptability of the proposed research in terms of institutional commitments (e.g., personnel and financial resources, adequacy of facilities) and applicable regulations, State and local law, or standards of professional conduct or practice; and
- Reports from any third party observations of the research carried out under 45 CFR 46.109(e).

5. Evaluating Research Progress

This section discusses three considerations for when the IRB evaluates the progress of a research study.

Confirmation that Continuing Review Information is Consistent with the IRB-approved Protocol

The IRB should confirm that the information provided by the investigator at the time of continuing review is consistent with the research protocol previously approved by the IRB. Information suggesting that the investigator is not conducting the research in accordance with either the IRB-approved protocol or the requirements or determinations of the IRB should prompt the IRB to defer re-approving the research and seek an explanation from the investigator regarding the apparent discrepancies.

Total Subject Enrollment

As part of its initial review of a research project, the IRB typically will have approved a protocol that includes the expected total number of subjects to be enrolled by the investigator and the expected rate of enrollment. Evaluating information about the number of subjects enrolled in the research at the time of continuing review may allow the IRB to ascertain whether enrollment is consistent with the planned number of subjects described in the IRB-approved protocol. A marked difference between the actual and expected rates of enrollment may indicate a problem with the research project that requires further evaluation, including whether the research project is likely to provide sufficient data to answer the scientific question(s) being posed.

Once the enrollment goals for the research project have been reached, the investigator should reassess the project to determine if data are indeed sufficient to answer the scientific questions raised by the research project. If the data are insufficient, it may be appropriate for the investigator to seek approval to amend the protocol by increasing the target for expected total subject enrollment. An investigator enrolling more subjects than the maximum number allowed under the IRB-approved protocol would represent a violation of (a) the constraints set forth by the IRB under its approval, and (b) the HHS regulatory requirement that all changes in a research activity not be initiated without IRB review and approval except when necessary to eliminate apparent immediate hazards to the subjects (45 CFR 46.103(b)(4)).

On the other hand, if enrollment in the research project is occurring at a much slower rate than expected and there are concerns about enrolling enough subjects to provide sufficient data to answer the scientific question(s) being addressed, it may not be ethical to continue exposing subjects to the risks of the research. To address low enrollment issues, an IRB may recommend that the reasons for the lagging enrollment be explored by the investigator (and any research sponsor or monitoring entity) and appropriate steps taken to remedy the situation (e.g., proposals for modification of recruitment practices, adjustment of inclusion criteria, etc.). In the absence of an adequate plan to remediate the lagging enrollment, the IRB may determine that the research should not be re-approved because the risks to subjects are not reasonable in relation to the anticipated benefits to the subjects and the importance of the knowledge that may reasonably be

expected to result (45 CFR 46.111(a)(2)) (see section D.1 below for additional guidance regarding the consideration by the IRB of subject enrollment in multicenter research projects).

Finally, in addition to assessing total subject enrollment at the time of continuing review, it also may be appropriate for the IRB to consider assessing the distribution of enrolled subjects by sex, race, ethnicity, or any other relevant demographic factors, taking into account variations in the prevalence of any disorder or condition under study across different demographic groups. Such information may be pertinent to the IRB's determination regarding whether selection of subjects is equitable and whether the research project is likely to provide sufficient data to answer the scientific question(s) being posed (45 CFR 46.111(a)(2) and (3)). For multicenter research projects, a central IRB (see section D.2 below) or a monitoring entity likely would be in the best position to assess the distribution of enrolled subjects by sex, race, ethnicity, or any other relevant demographic factor.

Subject Withdrawals

Subjects discontinue their participation in research for various reasons (e.g., serious adverse events, conflicts with the investigators, transportation problems, etc.).

The IRB's continuing review procedures in general should provide for review of:

- The number of subjects who discontinued their participation; and
- A summary of the reasons for the withdrawals, if known.

IRB review of this information may shed light on problems related to the conduct of the research. For example, a high rate of subject withdrawal secondary to serious adverse events may indicate that the risks of the research are greater than expected and may lead the IRB to conclude that the research should not be approved for continuation because the risks to subjects are not being minimized or are not reasonable in relation to the anticipated benefits to the subjects and the importance of the knowledge that may reasonably be expected to result (45 CFR 46.111(a)(1) and (2)).

In addition, as with a lower than expected enrollment rate, if there is a higher than expected rate of subject withdrawal, it may not be ethical to continue exposing subjects to the risks of the research because the project may not provide sufficient data to answer the scientific question. To address such circumstances, an IRB may recommend that the reasons behind the high withdrawal rate be explored by the investigator (and any research sponsor) and appropriate steps taken to remedy the situation. In the absence of an adequate plan to remediate the high withdrawal rate, the IRB may determine that the research should not be re-approved because the risks to subjects are not reasonable in relation to the anticipated benefits to the subjects and the importance of the knowledge that may reasonably be expected to result (45 CFR 46.111(a)(2)).

C. Process for Conducting Continuing Review

1. Key Procedural Requirements for Continuing Review Conducted by the IRB at Convened Meetings

Continuing review must take place at a convened meeting at which a majority of the IRB members are present, including at least one member whose primary concerns are in nonscientific areas, unless the research qualifies for review under an expedited review procedure (45 CFR 46.108(b)). In order for research undergoing continuing review to be approved by the IRB at a convened meeting, it must receive the approval of a majority of those members present at the meeting (45 CFR 46.108(b)). 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 for research projects undergoing continuing review unless the quorum can be restored (45 CFR 46.108(b)).

For each research project undergoing continuing review, the minutes of IRB meetings must be in sufficient detail to show 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 the research; and a summary of the discussion of controverted issues and their resolution. (45 CFR 46.115(a)(2)). In order to document the continued existence of a quorum, OHRP recommends that votes on actions taken by the IRB on research projects undergoing continuing review be recorded in the minutes using the format shown in the following examples:

- Total = 15 with no recusals; Vote: For-14, Opposed-0, Abstained-1.
- Total = 14 (one member recused); Vote: For-12, Opposed-2, Abstained-0.

Finally, the IRB must ensure that no member participates in the IRB's continuing review of any research project in which the member has a conflicting interest, except to provide information requested by the IRB (46 CFR 46.107(e)).

2. Key Procedural Requirements for Continuing Review Conducted Under an Expedited Review Procedure

When continuing review of research is conducted under an expedited review procedure, the review must be conducted by the IRB chairperson or one or more experienced reviewers designated by the IRB chairperson from among the IRB members (45 CFR 46.110(b)). The IRB chairperson must ensure that no IRB member participates in the expedited review of research in which the member has a conflicting interest, except to provide information requested by the chairperson or his/her designee(s) (46 CFR 46.107(e)). The IRB chairperson or IRB members designated by the chairperson only can approve or require modification in (to secure approval of) research, but may not disapprove research using the expedited procedures (45 CFR 46.110(b)). Disapproval of a research project at the time of continuing review can only occur after review by the IRB at a convened meeting, not by the expedited review process. All IRB members must be advised of research that has been approved under an expedited review procedure (45 CFR 46.110(c)).

See section E below for additional guidance regarding when an expedited review procedure may be used to conduct continuing review.

3. Written Procedures for Conducting Continuing Review

An institution (or when appropriate an IRB) must prepare and maintain – and the IRB must follow – written procedures for the continuing review of research (45 CFR 46.103(b)(4), 46.108(a), and 46.115(a)(6)). OHRP recommends that written procedures for continuing review describe the following:

- The procedures for informing investigators about their responsibilities related to continuing review under the HHS regulations at 45 CFR part 46 and the IRB’s own policies and procedures on continuing review requirements;
- The list of documents to be submitted by investigators at the time of continuing review, the time frame for submitting these documents to the IRB, and the procedure for requesting these documents from the investigator (see sections C.4 and G below for further guidance);
- The list of specific documents distributed or made available to primary reviewers (if applicable) and to all other IRB members (see sections C.4 and C.5 below for further guidance);
- Any primary reviewer system used (see section C.6 below for further guidance);
- Any process (e.g., an administrative review process by IRB staff or a subcommittee review procedure) that may be used to supplement the IRB’s continuing review (see section C.7 below for further guidance);
- For research requiring continuing review at a convened meeting, the timing of document distribution prior to IRB meetings;
- The range of possible IRB actions taken on research projects undergoing continuing review (see section C.9 below for further guidance);
- How continuing review under an expedited review procedure is conducted and how expedited approval actions are communicated to all IRB members;
- The procedures for:
 - Communicating to investigators IRB actions regarding continuing review of research and any changes or clarifications required by the IRB as a condition of IRB approval; and
 - Reviewing and acting upon investigators’ responses to the IRB’s requests for changes or clarifications;
- Which institutional office(s) and official(s) are notified of IRB findings and actions regarding continuing review and how notification to each is accomplished;
- The procedures for how the IRB determines the effective date of IRB approval following initial review of a research study and communicates this effective date and the initial period of approval to the investigator (see section G below for guidance regarding how to determine the effective date of initial IRB approval);
- The procedures for how the IRB determines continuing review dates for a research study (including whether the IRB follows a procedure for maintaining fixed anniversary dates for the expiration of annual IRB approvals) and communicates the period of approval

- 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; see section F below for additional guidance on determining the frequency of continuing review); and
- 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 at 45 CFR part 46 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).

4. Submission of Documents to the IRB

Investigators are responsible for fulfilling requirements associated with continuing review in time for the IRB to carry out continuing review prior to the expiration date of the current IRB approval. In particular, investigators are responsible for submitting sufficient materials and information for the IRB to meet its regulatory obligations, and should follow the institutional policies and procedures for continuing IRB review of research that are required by 45 CFR 46.103(b)(4) and referenced in the institution's OHRP-approved Federalwide Assurance (FWA). OHRP recommends that institutions have written procedures for continuing review that require investigators to submit the following documents, as applicable, if not already available to the IRB as part of the existing IRB records for the research:

- A brief project summary (this could be included as part of a progress report described in the next bullet, provided as a separate document, or be addressed by referencing other documents made available to the IRB, including the informed consent document(s));
- A progress report that includes the following:
 - The number of subjects accrued;
 - A brief summary of any amendments to the research approved by the IRB since the IRB's initial review or the last continuing review;
 - Any new and relevant information, published or unpublished, since the last IRB review, especially information about risks associated with the research (note that OHRP does not expect the IRB to perform an independent review of the relevant scientific literature related to a particular research project undergoing continuing review; this responsibility rests with the investigators and any monitoring entity for the research);
 - A summary of any unanticipated problems and available information regarding adverse events (the amount of detail provided in such a summary will vary depending

- on the type of research being conducted; in many cases, such a summary could be a 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 investigator's brochure (if applicable));
- A summary of any withdrawal of subjects from the research since the last IRB review, and the reasons for withdrawal, if known; and
 - A summary of any complaints about the research from subjects or others since the last IRB review;
 - The latest version of the protocol and informed consent document(s);
 - Any proposed modifications to the informed consent document or protocol;
 - For FDA-regulated research, the Investigator's Brochure, if available, including any modifications; and
 - Any other significant information and documents, such as reports from DSMBs or DMCs, that are available.

In developing procedures for continuing review, the IRB might consider use of templates, checklists, or other tools to standardize the request for information or list of materials to be provided to the IRB by investigators at the time of continuing review.

5. Distribution and Availability of Documents for Review by IRB Members

An IRB that is conducting continuing review of research should be familiar with, and have access to, all IRB records related the research, including those associated with the initial review and approval and any other previous reviews, including ad hoc and scheduled continuing reviews and any reviews of amendments to the research or unanticipated problems.

OHRP recommends that for continuing review of a research study not eligible for expedited review all IRB members receive and review copies of the progress report described in the preceding section, the current IRB-approved informed consent document, and any newly proposed consent document. At least one member of the IRB (i.e., a primary reviewer; see next section) should have available, for review as needed, the complete IRB file, including the complete protocol, relevant IRB meeting minutes, and any additional documents submitted by the investigator with the continuing review progress report. The complete IRB file also should be made available upon request to any IRB member prior to the meeting at which the research is to be reviewed and should be accessible during the meeting to allow members to resolve any questions that may arise during the IRB's deliberations.

When conducting continuing review of research under an expedited review procedure, the IRB chairperson (or designated IRB member(s)) should receive and review copies of the progress report described in the preceding section, the current IRB-approved informed consent document, and any newly proposed consent document, and have available, for review as needed, all of the above-referenced documentation, including the complete IRB protocol file.

6. Primary Reviewers

IRBs may adopt a variety of procedures to reduce burdens and allow the IRB to efficiently accomplish its continuing review workload. One such commonly-adopted procedure is the use of primary reviewers for continuing review of research at convened IRB meetings. Primary reviewers are members of the IRB with appropriate expertise typically designated to perform primary review of IRB records related for research undergoing continuing review, provide a summary to the other IRB members, and lead the discussion at the convened IRB meeting. The primary reviewer's summary might highlight any critical issues for consideration by the IRB, identify any key changes being proposed by the investigator, and include recommendations for action by the IRB. A typical primary reviewer's summary might note that no issues of concern have arisen since the prior IRB review, no changes are being proposed by the investigator, adverse events are of the type and frequency expected, the research appears to satisfy all criteria required for approval under 45 CFR 46.111 (and subparts B, C, and D when applicable), and the primary reviewer recommends approval without any stipulated changes.

7. Involvement of IRB Staff in Preliminary Review

Appropriately trained IRB staff members, regardless of whether they are members of the IRB, may perform preliminary reviews of continuing review documents and complete IRB files in order to facilitate the continuing review of research by the IRB. As part of this preliminary review, IRB staff may perform the following functions, among others:

- Confirm that all documents required by the IRB have been submitted by the investigator;
- Assess whether the information and documents submitted by the investigator are consistent with the research protocol previously approved by the IRB;
- Confirm that the informed consent document submitted by the investigator matches the current IRB-approved informed consent document;
- Identify important issues and concerns that the IRB may wish to consider; and
- Provide technical assistance and guidance to the IRB at convened meetings and to the IRB chairperson (or designated IRB member(s)) during an expedited review process.

IRB staff members who are *not* IRB members may not be delegated responsibility for making the determinations that must be made by the IRB at the time of continuing review (see sections B, C.1 and C.2 above) and may not approve research on behalf of the IRB (45 CFR 46.109).

8. Procedures for Continuing Review Deliberations During IRB Meetings

Research studies undergoing continuing review by the IRB at convened meetings should be considered and discussed individually. Furthermore, OHRP recommends that the IRB act and vote on research studies individually. If an IRB adopts a procedure under which the IRB votes on groups of studies undergoing continuing review, such a procedure must provide IRB members with the ability to vote "yes" on some studies, "no" on others, and abstain on others (45 CFR 46.108(b)).

As previously noted, no IRB member may participate in the review of research in which the member has a conflicting interest, except to provide information requested by the IRB (45 CFR 46.107(e)). Individual consideration of, and voting on actions related to, research projects during continuing review will help to ensure that members with a conflicting interest related to a particular study do not participate in the IRB's continuing review of that study, except to provide information requested by the IRB.

OHRP recommends that minutes of IRB meetings document by name any member who had a conflicting interest in a research study and therefore was excluded from participation in the IRB's continuing review of that study, except to provide any information requested by the IRB. OHRP further 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 conducts continuing reviews of research in which they have a conflicting interest, and that such also be noted in the minutes of the IRB meeting.

When conducting continuing review of a research project, the IRB, at its discretion, may invite individuals with competence in special areas to assist in the review of issues which require expertise beyond or in addition to that available to the IRB. The input of such expert consultants may be provided through (a) submission of written reports to the IRB prior to the IRB meeting at which a research project for which consultation was sought is to be reviewed and/or (b) the attendance and participation (either in person or by telephone or videoconference) of the expert consultants in the deliberations at the IRB meeting. These individuals may not vote with the IRB (45 CFR 46.107(f)), and their attendance at an IRB meeting must be documented in the minutes of the IRB meeting if they attend the meeting (45 CFR 46.115(a)(2)). OHRP recommends that the minutes of the meeting also document the role any expert consultant played in the IRB's review.

The amount of time the IRB spends on the continuing review of a particular research project at a convened meeting will vary depending on the nature and complexity of the research, the amount and type of new information presented to the IRB by the investigator, and whether the investigator is seeking approval of substantive changes to the research protocol or informed consent document. For many research projects, continuing review can be fairly straightforward, and the IRB should be able to complete its deliberations and approve the research within a brief period of time.

For example, consider the continuing review by the IRB of a randomized clinical trial for which the investigator reports the following:

- The research is proceeding in accordance with the IRB-approved protocol;
- The rate of subject enrollment is as expected;
- There have been no unanticipated problems;
- The rate and pattern of adverse events is as expected;
- No subjects have complained about the conduct of the research or withdrawn from the research;

- There is no new published or unpublished information that would alter the IRB's prior determinations, particularly with respect to the IRB's prior evaluation of the potential benefits and risks to the subjects and the informed consent process; and
- No changes to the protocol or informed consent document are needed.

In the absence of any concern about the research being raised by the IRB member assigned to be the primary reviewer or by any other IRB member present at the IRB meeting, the IRB should be able to complete its continuing review deliberations for such a research project within a brief period of time. In this example, deliberations that included the following brief series of steps would be sufficient:

- The primary reviewer provides a brief synopsis of the research and a statement that:
 - No concerning issues have arisen since the prior IRB review and approval;
 - No changes to the project are being proposed by the investigator;
 - Adverse events in subjects have been of the type and frequency expected;
 - The research appears to continue to satisfy all criteria for approval under the regulations at 45 CFR 46.111 (and subparts B, C, and D, when applicable); and
 - The reviewer recommends approval without any conditions.
- The IRB chairperson calls for a motion on the project;
- The primary reviewer makes a motion to approve the research without conditions and another member seconds the motion;
- The IRB chairperson makes a request for discussion by the IRB members; and
- Following any discussion, the IRB chairperson calls for a vote on the motion to approve the project without conditions.

On the other hand, consider the continuing review of a randomized clinical trial for which the investigator reports the following:

- The rate of serious adverse events occurring in subjects is significantly higher than expected;
- A recently completed research project reported in the literature identified previously unrecognized risks for the same experimental intervention being tested in the clinical investigator undergoing continuing review;
- The investigator is proposing several substantive revisions to the protocol in response to the new risk information, including the addition of new exclusion criteria and new safety monitoring procedures for subjects; and
- The investigator is proposing substantive changes to the informed consent document to add a description of the new information regarding reasonably foreseeable risks.

In these circumstances the IRB would need to spend significantly more time at the convened meeting on its continuing review of the research as it carefully reassesses whether the risks to subjects still are minimized and reasonable in relation to the to anticipated benefits, if any, to the subjects and the knowledge that is expected to result, given the new information presented by the investigator. The IRB also would need to assess whether the changes to the protocol and

informed consent document proposed by the investigator are appropriate and adequate, or whether additional changes should be required.

9. Approving Research with Conditions at the Time of Continuing Review

Given the authorities that IRBs have under HHS regulations at 45 CFR 46.109(a), when conducting either initial or continuing review of a research study, an IRB can take any of the following actions:

- Approve the research study as submitted without any conditions;
- Approve the research study with conditions;
- Defer or table the research study for further review at a future date (see section H for a discussion of how to handle lapses in IRB approval); or
- Disapprove the research study.

With respect to the second action listed above, IRBs sometimes approve research with conditions. By *IRB approval with conditions* in the context of continuing review, OHRP means that at the time when the IRB reviews and re-approves a research study, the IRB as a condition of approval requires that the investigator (a) make specified changes to the research protocol or informed consent document(s), or (b) submit clarifications or additional documents, such that, based on the assumption that the conditions are satisfied, the IRB is able to make all of the determinations required for approval under the HHS regulations at 45 CFR 46.111 and, if applicable, subparts B, C or D of 45 CFR part 46. With respect to research reviewed and approved with conditions by the IRB at a convened meeting, note that because the IRB is able to make all these determinations, the IRB may designate the IRB chairperson (and/or other individual(s)) to review responsive materials from the investigator and determine that the conditions have been satisfied, and further review by the IRB at a subsequent convened meeting would not be necessary.

When approving research with conditions at the time of continuing review, the IRB should be careful to specify whether any conditions need to be satisfied before an investigator can continue particular research activities related to those conditions. For example, if at the time of continuing review, the IRB requires the investigator to change the research protocol to include a specific new procedure for screening prospective subjects, the IRB could approve the research with the following condition: research activities involving currently enrolled subjects may continue, but no new subjects may be enrolled until a designated IRB member reviews a revised protocol and verifies that the protocol includes the new screening procedure.

For guidance regarding how to determine the effective date of initial IRB approval and the subsequent continuing review dates, see section G below. For additional guidance on IRB approval of research with conditions, see OHRP's draft *Guidance on IRB Approval of Research With Conditions* at <http://www.hhs.gov/ohrp/requests/>.

10. Additional Considerations Regarding Continuing Review Using an Expedited Review Procedure

When conducting continuing review under an expedited review procedure, the IRB chairperson or other member(s) designated by the chairperson, at their discretion, may invite individuals with competence in special areas to assist in the review of issues which require expertise beyond or in addition to that available to the IRB (45 CFR 46.107(f)). OHRP recommends that in such cases the IRB records document the involvement of such expert consultants in the expedited review. However, only the IRB chairperson or experienced IRB members designated by the chairperson may carry out continuing review and approve research under the expedited review procedure.

An IRB administrator or staff member who is also an experienced member of the IRB may be designated by the IRB chairperson to conduct continuing review of research under an expedited review procedure.

OHRP also recommends that documentation for continuing reviews conducted under an expedited review procedure include:

- The specific categories permitting the expedited review; and
- Documentation of the review and action taken by the IRB Chairperson or designated reviewer.

See section E below for additional guidance regarding when an expedited review procedure may be used to conduct continuing review and recommendations regarding using an expedited review procedure to conduct continuing review when the only remaining human subjects research activities are limited to data analysis.

11. Using a Different IRB to Conduct Continuing Review

The IRB that conducted the initial review of a research project may be best suited to conduct continuing review of that project because of its familiarity with the research. However, an IRB other than the one that conducted the initial or other prior reviews of a research project may conduct continuing review of the project, as long as the IRB conducting the continuing review has members with appropriate experience and expertise and access to all prior relevant IRB records.

OHRP is aware that some institutions have designated one or more IRBs for the sole purpose of conducting continuing review. Such a practice is permissible under the HHS regulations for the protection of human subjects at 45 CFR part 46, as long as such IRBs satisfy the IRB membership requirements under 45 CFR 46.107 and fulfill the regulatory requirements for conducting continuing review referenced in this document.

D. Additional Considerations for Continuing Review of Multicenter Research Projects

When the HHS human subjects protection regulations at 45 CFR part 46 were first issued in 1974, the single investigator-single institution project was the norm, and reporting requirements to IRBs were almost entirely and appropriately fulfilled by the investigator, who was in a position to know about all aspects of the research project. Since that time, research projects involving multiple institution (hereafter referred to as “multicenter research projects”) have become commonplace. Although an individual investigator at a particular institution involved in a multicenter research project informs the local IRB at that institution about events related to subjects enrolled at that institution, the investigator and IRB are not likely to be well-informed about the progress of the research project across all institutions involved in the research. Consequently, IRB review and oversight of such research has become more challenging.

1. Multiple Institutions Relying on Local IRBs for Continuing Review

For many multicenter research projects, most institutions involved in the research choose to rely upon an internal IRB operated by the institution (hereinafter referred to as a “local IRB”) for both initial and continuing review of such projects.

As noted above in section C.4, OHRP recommends that institutions have written procedures for continuing review that require investigators to submit to the IRB at the time of continuing review a progress report that includes, among other things, summaries of any unanticipated problems, available information regarding adverse events, and any withdrawals of subjects or complaints about the research from subjects or others since the last IRB review. For continuing review of multicenter research at a particular institution, OHRP recommends that the local investigator include in the progress report a summary of such events for subjects who participated at that institution.

OHRP recognizes that local investigators participating in multicenter research projects usually are unable to prepare a meaningful summary of project-wide information, including information on adverse events, subject withdrawals, and complaints about the research, for their local IRBs because such project-wide information is not readily available to them. In such circumstances, when the research project 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 local IRBs the most current report from the monitoring entity, if available. Such monitoring entities are in the unique position of having information for the entire project that may assist the IRBs in reviewing the research and protecting subjects. OHRP further recommends that such reports include the following:

- A statement indicating what information (e.g., project-wide adverse events, subject withdrawals, complaints about the research, interim findings, and any recent literature that may be relevant to the research) was reviewed by the monitoring entity;
- The date of the review; and
- The monitoring entity’s assessment of the information reviewed.

The local IRB has authority to require that such a report be submitted by the investigator and also may ask the monitoring entity directly to provide such a report (45 CFR 46.102(h) and 46.109(a)).

As discussed in section B.5 above, the IRB should evaluate information about the number of subjects enrolled in the research at the time of continuing review because a marked difference between the actual and expected rates of enrollment may indicate a problem with the project that requires further evaluation. When the local IRB at one institution is evaluating subject enrollment based on information provided by the local investigator, it may discover a much lower than expected rate of enrollment at that institution. In the absence of project-wide data being available to the IRB, such information may be indicative of lagging enrollment at that one local institution or at all institutions. In these circumstances, the local IRB should consider seeking additional information regarding project-wide enrollment. Project-wide enrollment data may indicate that there is sufficient rationale to continue the research project at the local institution despite low local enrollment because project-wide enrollment is progressing at the expected rate. Similar considerations would also apply to the local IRB's review of local subject withdrawals.

For any particular institution that chooses to rely upon a local IRB, continuing review of a multicenter research project by the designated local IRB at that institution must occur at least annually as long as the institution remains engaged in human subjects research activities involving the project (45 CFR 46.109(e)). Once the institution is no longer engaged in human subjects research activities under the project, there is no need for continuing review by the local IRB, even if human subjects research activities are occurring at other institutions. For example, consider a multicenter clinical trial in which the following conditions exist with respect to institution A:

- The research is permanently closed to enrollment at the institution;
- All subjects enrolled at the institution have completed all-research related interventions and interactions, including interventions and interactions related to collection of long-term follow-up data;
- No additional identifiable private information about the subjects is being obtained by investigator at the institution; and
- All data that includes identifiable private information about the subjects enrolled at that institution has been submitted to the statistical center at another institution for analysis.

In these circumstances, the local IRB for institution A does not need to conduct any additional continuing review of the research project. On the other hand, the local IRBs relied upon by other institutions where investigators continue to enroll subjects, intervene or interact with subjects, obtain identifiable private information about subjects, or analyze identifiable private information in accordance with the IRB-approved protocol would need to conduct continuing review of the research project at least annually.

2. Implementation of Cooperative IRB Review Arrangements for Continuing Review, Including Use of Central IRB Procedures

In the conduct of multicenter research projects, each institution engaged in the project is responsible for safeguarding the rights and welfare of human subjects and for complying with the requirements of 45 CFR part 46 (45 CFR 46.114). For multicenter research projects, an institution participating in the project may enter into a joint IRB review arrangement, rely on the review of a qualified IRB at another participating institution, or make similar cooperative IRB review arrangements for avoiding duplication of effort (45 CFR 46.114). These cooperative IRB review arrangements can be used for both initial and continuing review. OHRP encourages institutions engaged in multicenter research projects to utilize cooperative IRB review arrangements whenever it is appropriate and feasible to do so.

When an institution holding an OHRP-approved FWA relies upon an IRB operated by another institution or organization (i.e., an “external IRB”) to review HHS-conducted or -supported research, the institution holding the FWA must designate the external IRB on its FWA and must execute an IRB Authorization Agreement (see <http://www.hhs.gov/ohrp/humansubjects/assurance/iprotsup.rtf>) with the institution or organization operating the designated IRB (45 CFR 46.103(a) and 46.103(b)(2); also see the Terms of the FWA at <http://www.hhs.gov/ohrp/humansubjects/assurance/filasurt.htm>). Furthermore, when review responsibilities for a multicenter research project are shared across multiple IRBs under a cooperative review arrangement, OHRP recommends that the IRB Authorization Agreements or other written documents identify the responsibilities covered by the agreement and who is responsible for them.

It is important to note that each institution holding an OHRP-approved FWA has a responsibility to ensure that the IRBs designated under the FWA collectively possess sufficient knowledge of the local research context for the research that they review on behalf of the institution.

Cooperative IRB review arrangements for a multicenter research project may vary with respect to how continuing review will be carried out. For example, all institutions engaged in a multicenter research project could designate the same IRB to conduct all aspects of continuing review on behalf of all institutions. Alternatively, all institutions engaged in a multicenter research project could designate the same IRB to have primary responsibility for continuing review of the research with respect to the assessment of project-wide information, but assign responsibility for assessment of local issues to each institution’s designated local IRB. In both examples, the IRB that all institutions rely upon either partially or completely is commonly referred to as a “central IRB.”

During its continuing review of a multicenter research project, a central IRB typically is responsible for reviewing a standard, project-wide protocol and the model/template informed consent document(s) that are distributed to investigators at all institutions engaged in the research. Depending on the nature of the cooperative IRB review arrangement, a central IRB at the time of continuing review also may be responsible for reviewing and approving the actual informed consent documents in use at one or more (or even all) institutions. If a central IRB

conducting continuing review is responsible for the assessment of local issues, the central IRB may supplement its procedures as appropriate to ensure that local issues are addressed. For example, a central IRB may ask the local investigators or institutional officials for each institution relying on the central IRB to provide information related to subject withdrawals or complaints about the research. A central IRB's review of this information may shed light on problems related to the conduct of the research at a particular institution.

Whenever multiple institutions rely upon a central IRB to conduct continuing review of a multicenter research project that is overseen by a monitoring entity (e.g., the research sponsor, a coordinating or statistical center, or a DSMB/DMC the project sponsor), OHRP recommends that the central IRB obtain a report describing project-wide information from that monitoring entity. Such monitoring entities are in the unique position of having information for the entire project that may assist the IRB in reviewing the research project and protecting subjects. The central IRB has authority to require that such a report be submitted by the investigators and also may ask the monitoring entity directly to provide such a report (45 CFR 46.102(h) and 46.109(a)). OHRP recommends that such reports include the same information as noted in section D.1 above.

E. When Expedited Review Procedures May Be Used by an IRB for Continuing Review

1. General Considerations

IRBs may use an expedited review procedure to conduct continuing review of research projects that:

- Involve only procedures described in one or more of the nine categories of research activities published in the Federal Register (see 63 FR 60364-60367, November 9, 1998, available at <http://www.hhs.gov/ohrp/humansubjects/guidance/expedited98.htm>); and
- Are found by the reviewers to involve no more than minimal risk to the subjects (45 CFR 46.110(b)).

Expedited review categories (1) to (7) apply to both initial and continuing review, whereas expedited review categories (8) and (9) apply only to continuing review.

In general, a research study that was eligible for initial review under an expedited review procedure will qualify for an expedited review procedure at the time of continuing review. However, IRBs should be aware that a research study previously approved under an expedited review procedure in some circumstances will need to undergo continuing review by the IRB at a convened meeting. For example, the investigator at the time of continuing review may propose changes to the research project that involve the addition of activities that do not fall within the scope of any of the categories of research activities eligible for an expedited review procedure.

Likewise, a research project that was *not* eligible for initial review under an expedited review procedure usually will *not* qualify for an expedited review procedure at the time of continuing review, except in the following limited circumstances:

- The research project involves only activities described by expedited review categories (8) or (9); or
- Research project previously approved by the IRB at a convened meeting progresses to the stage where all of the remaining human subjects research activities involve no more than minimal risk to the subjects and fall within the scope of one or more of expedited review categories (2) through (7).

2. Expedited Review Category (8)

Under category (8), an expedited review procedure may be used for the continuing review of research previously approved by the IRB at a convened meeting 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.

For a multicenter research project, an expedited review procedure may be used by the IRB for a particular institution whenever the conditions of category (8)(a), (b), or (c) are satisfied for that institution. As a result, for some institutions involved in the conduct of a multicenter research project, the IRBs reviewing the project may need to conduct continuing review of the project at a convened meeting, whereas for other institutions, the IRBs may conduct continuing review using an expedited review procedure under category (8). With respect to category (8)(b), while the criterion that “no subjects have been enrolled” is interpreted by OHRP to mean that no subjects have ever been enrolled at a particular institution, the criterion that “no additional risks have been identified” is interpreted to mean that neither the investigator nor the IRB at a particular institution has identified any additional risks from any institution engaged in the research project or from any other relevant source since the IRB’s most recent prior review.

Expedited review category (8)(a) and the meaning of “long-term follow-up”

Under expedited review category (8)(a), OHRP interprets “long-term follow-up” to include:

- Research *interactions* that involve no more than minimal risk to subjects (e.g., quality of life surveys or the obtaining of survival data); and
- Collection of follow-up data from procedures or interventions that would have been done as part of routine clinical practice to monitor a subject for disease progression or recurrence, regardless of whether the procedures or interventions are described in the research protocol.

In contrast, OHRP interprets “long-term follow-up” to exclude:

- Research *interventions* that would not have been performed for clinical purposes, even if the research interventions involve no more than minimal risk (e.g., blood draws).

However, some research studies that are not eligible for expedited review under category (8)(a) at the time of continuing review may be eligible for expedited review under one of the other expedited review categories. For example, if a research project's only remaining activity involves long-term follow-up of subjects by drawing 15 ml of blood once annually for a test that is not part of routine clinical practice, such research would not be eligible for expedited review under category (8)(a), but might be eligible for expedited review under category (2).

Expedited review category (8)(c) and data analysis

OHRP considers a research study to continue to involve *human subjects* as long as the investigators conducting the research continue to obtain: (1) data about the subjects of the research through intervention or interaction with them; or (2) identifiable private information about the subjects of the research (45 CFR 46.102(f)). OHRP interprets *obtaining identifiable private information* to include an investigator's use, study, or analysis of identifiable private information. Therefore, as long as a non-exempt human subjects research study continues to involve use, study, or analysis of identifiable private information by the investigators, the research continues to involve human subjects and must undergo continuing review by an IRB at least annually (45 CFR 46.109(e)), even if the participation of all subjects in a research project has been completed or discontinued.

Under expedited review category 8(c), an IRB may use an expedited review procedure to conduct continuing review when the only remaining human subjects research activity is the analysis of data that includes identifiable private information and the IRB chairperson (or another experienced IRB member designated by the chairperson) determines that this activity involves no more than minimal risk. OHRP expects that in nearly all cases such research activities will involve no more than minimal risk and therefore be eligible for IRB review under an expedited review procedure.

OHRP notes that the process for conducting continuing review of research under expedited review category (8)(c) can be accomplished through a simple, abbreviated process. For example, the investigator, as part of the continuing review process, could provide to the IRB the following statement regarding the research: "the study only involves data analysis, which is proceeding in accordance with the IRB-approved research protocol, and there are no problems to report." This statement could be provided by email or as part of a standard continuing review application form. Upon receipt of such a statement from the investigator, the IRB chairperson, or other member(s) designated by the chairperson, under the expedited review procedure may approve the continuation of the research project for another year without further deliberation or review.

For a multicenter research project, only the institution engaged in the ongoing data analysis activities (e.g., the institution operating the coordinating center or statistical center for the research project) needs to ensure that continuing review of the research by an IRB designated under the institution's FWA occurs at least annually. Furthermore, when the data analysis activities progress to the point when they no longer involve analysis of identifiable private information, further continuing review of the research is no longer required.

3. Expedited Review Category (9)

Under category (9), an expedited review procedure may be used for the continuing review of research previously approved by the IRB at a convened meeting that meets the following conditions:

- The research is not conducted under an investigational new drug application (IND) or an investigational device exemption (IDE);
- Expedited review categories (2) through (8) do not apply to the research;
- The IRB has determined and documented at a convened meeting that the research involves no greater than minimal risk to the subjects; and
- No additional risks of the research have been identified

With regard to the third condition, the IRB at a convened meeting must have determined that either (a) the research project as a whole involved no more than minimal risk, or (b) the remaining research activities involving human subjects present no more than minimal risk to the subjects. With regard to multicenter research projects, the fourth condition that “no additional risks have been identified” is interpreted to mean that neither the investigator nor the IRB at a particular institution has identified any additional risks from any institution engaged in the research project or from any other relevant source since the IRB’s most recent prior review.

The following are two examples of research eligible for expedited review under category (9):

- A research study is designed to evaluate the effects of urban pollution on pulmonary status in healthy adults. The study is not conducted under an IND or IDE. The subjects are healthy adult volunteers living in urban settings who are asked to undergo monthly surveys regarding outdoor exercise activities and pulmonary symptoms, annual pulmonary function tests measured by routine spirometry procedures, and annual chest x-rays for five years. At the time of initial review, the IRB reviewed and approved the research at a convened meeting and determined and documented that the research involves no more than minimal risk. Because of the annual chest x-ray, the research at the time of initial review did not qualify for review under expedited review categories (1) through (7); in particular, category (4) explicitly excludes procedures involving x-rays. At the time of the first continuing review, the IRB chairperson determines that the research continues to involve no more than minimal risk and that there have been no additional risks identified since the initial review. Therefore, the research study may undergo continuing review under expedited review under category (9).
- A research study is designed to evaluate the fluctuations in inflammatory cytokines in the serum of adult patients with newly diagnosed rheumatoid arthritis. The study is not conducted under an IND or IDE, and management of the subject’s rheumatoid arthritis is determined clinically by the subject’s primary rheumatologist and not by the investigator. The subjects are asked to undergo collection of 30 ml of blood by venipuncture 4 times per week for 6 weeks for measurement of serum inflammatory cytokines. The investigator plans to enroll 30 subjects per year for 3 years. At the time of initial review, the IRB reviewed and approved the research at a convened meeting and determined and

documented that the research involves no more than minimal risk. Because of the frequency of blood collection, the research did not qualify at the time of initial review for review under expedited review categories (1) through (7); in particular, the frequency of blood draws exceeds that permitted under category (2). At the time of the first continuing review, the IRB chairperson determines that the research continues to involve no more than minimal risk and that there have been no additional risks identified since the initial review. Therefore, the research may undergo continuing review under expedited review under category (9).

For additional guidance on the process for conducting continuing review of research eligible for review under an expedited review procedure, see section C above.

F. Determining the Frequency of Continuing Review

The IRB must conduct 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)). In addition, the IRB must have and follow written procedures for conducting continuing review and for determining which projects require review more often than annually (45 CFR 46.103(b)(4) and 46.108(a)).

The IRB should decide the frequency of continuing review for each research project necessary to ensure the continued protection of the rights and welfare of research subjects. More frequent review (i.e., more frequently than once per year) may be appropriate, for example, when the risks to subjects warrants more frequent reassessment. OHRP recommends that the IRB consider the following factors when deciding on an appropriate interval for continuing review and that these factors be outlined in the IRB's written procedures for deciding the frequency of continuing review:

- The nature of any risks posed by the research project;
- The degree of uncertainty regarding the risks involved;
- The vulnerability of the subject population;
- The experience of the investigators in conducting research;
- The IRB's previous history with the investigators;
- The projected rate of enrollment; and
- Whether the research project involve novel interventions.

At the time of initial approval of a research project, the IRB should specify the duration of the approval period and the interval by which continuing review must occur (e.g., 4 months, 6 months, or 1 year) in order for the research to continue. OHRP notes that in addition to specifying a time interval, the IRB also may specify a subject enrollment number as a threshold for determining when continuing review is to occur. For example, at the time of initial review and approval of a high-risk clinical trial, the IRB might require that continuing review occur either in 6 months or after 5 subjects have been enrolled, whichever occurs first. OHRP also recommends that the minutes of IRB meetings clearly document the approval period (continuing review interval).

Similarly, OHRP recommends that at the time of continuing review the IRB consider whether the current frequency of continuing review for the research study is adequate or should be adjusted. For example, if the IRB initially approved a research study for a period of a year and at the first annual continuing review determined that the risks posed to the subjects have increased significantly, the IRB might re-approve the project after determining that the criteria for approval under 45 CFR 46.111 remain satisfied, but require that the next continuing review occur in 6 months.

The IRB's determinations regarding the approval of research and the required interval for continuing review must be communicated to the investigator in writing (45 CFR 46.103(b)(4) and 46.109(d)).

G. Determining the Effective Date of Initial IRB Approval and the Dates for Continuing Review

1. General Considerations

The IRB's written procedures should describe how the IRB (a) determines the effective date of IRB approval following initial review of a research study; (b) determines continuing review dates for a research study; and (c) communicates these dates and the periods of approval to the investigator.

In general, review of a proposed change to a research project during the period for which approval is authorized does not constitute continuing review of the project as a whole, and thus does not extend the date by which continuing review must occur (e.g., beyond one year from the effective date of the initial approval or the most recent continuing review approval).

2. Determining the *First* Continuing Review Date for Research Reviewed by the IRB at a Convened Meeting at the Time of Initial Review and Approved for One Year

Except when an expedited review procedure is used, the 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 (45 CFR 46.108(b)). In order for the research to be approved by the IRB at a convened meeting, it must receive the approval of a majority of those members present at the meeting (45 CFR 46.108(b)).

When the IRB Reviews and Approves Research *Without Conditions* at a Convened Meeting

When an IRB conducts the initial review of a research project at a convened meeting and approves the research for one year *without* requiring either (a) changes to the protocol or informed consent document(s), or (b) submission of clarifications or additional documents, the effective date of the initial approval is the date of that IRB meeting. In such circumstances, the **first** continuing review must occur within one year of the IRB meeting at which the research project initially was approved (45 CFR 46.109(e)).

An example of this scenario would be as follows:

- An IRB conducts initial review of a research project at a convened meeting on October 1, 2009 and approves the project for one year without requiring (a) any changes to protocol or informed consent documents, or (b) submission of any clarifications or additional documents. The effective date of the initial IRB approval would be October 1, 2009, and continuing review must occur within one year of the date of the IRB meeting, that is, by October 1, 2010.

*When the IRB Reviews and Approves Research **With Conditions** at a Convened IRB Meeting Without Requiring Further Review at a Subsequent Convened Meeting*

A much more common scenario is when an IRB conducting the initial review of a research project at a convened meeting takes the following set of actions:

- Approves the project for one year;
- As a condition of approval, requires either (a) changes to the protocol or informed consent document(s), or (b) submission of clarifications or additional documents; and
- Directs that the IRB chairperson (or other individual(s) designated by the IRB) to review and determine on behalf of the IRB whether the changes, clarifications, and/or additional documents to be submitted by the investigator(s) are satisfactory (see OHRP's draft *Guidance on IRB Approval of Research With Conditions* at <http://www.hhs.gov/ohrp/requests/>).

Under this scenario, further review by the IRB at a subsequent convened meeting is not necessary in order for the initial approval to become effective, and the effective date of the initial approval is the date on which the IRB chairperson (and/or any other individual(s) designated by the IRB) has reviewed and accepted as satisfactory all changes to the protocol or informed consent documents, or any other responsive materials, required by the IRB from the investigator. In such circumstances, the first continuing review must occur no later than one year after that effective date of initial IRB approval (45 CFR 46.109(e)). The IRB records must include documentation of the date when the IRB chairperson (and/or other individual(s) designated by the IRB) determined that all conditions of IRB approval have been satisfied, and the approval becomes effective (45 CFR 46.102(h) and 46.115(a)).

Examples of this scenario would be as follows:

- An IRB conducts an initial review of a research project at a convened meeting on October 1, 2009, approves the project for one year, and requires that the investigator make minor changes to the protocol as a condition of its approval. The IRB directs the IRB chairperson to review, on behalf of the IRB, the revised protocol and determine whether the changes required by the IRB have been made. On November 1, 2009, the IRB chairperson reviews the revised protocol and determines that the changes made by the investigator are satisfactory. The effective date of the initial IRB approval is

November 1, 2009, and the first continuing review must occur within one year of that date, that is, by November 1, 2010.

- An IRB conducts initial review of a research project at a convened meeting on October 1, 2009, and has serious concerns regarding the study design. The IRB defers taking action on the project and requires that the investigator submit a revised protocol in order to secure approval at a future IRB meeting. At a convened meeting on December 1, 2009, the IRB reviews a revised protocol, approves the research project for one year, and requires that the investigator make minor changes to the informed consent document and submit documentation of a co-investigator's hospital privileges as conditions of its approval. The IRB directs the IRB chairperson to review, on behalf of the IRB, (a) the revised informed consent document to determine whether the changes required by the IRB have been made, and (b) the documentation of the co-investigator's hospital privileges. On December 15, 2009, the IRB chairperson reviews the revised informed consent document and documentation of the co-investigator's hospital privileges, and determines that the changes made by the investigator to the informed consent document and the documentation of the co-investigator's hospital privileges are satisfactory. The effective date of the initial IRB approval is December 15, 2009, and the first continuing review must occur within one year of that date, that is, by December 15, 2010.

In circumstances where an IRB at a convened meeting approves a research study with conditions, OHRP recommends the following:

- The IRB should consider implementing administrative procedures to minimize the time between the IRB's review and approval of the research study at the convened meeting and the investigator's submission of revised protocol or informed consent documents or any other responsive materials requested by the IRB (e.g., the IRB might require, if appropriate, that (a) the investigator submit such materials within 90 days of the IRB meeting, and (b) if the investigator misses such a deadline, the research study be reviewed again by the IRB at another convened meeting upon receipt of the responsive materials from the investigator); and
- When responding after a prolonged period of time to the IRB's request for either (a) changes to the protocol or informed consent document(s), or (b) submission of clarifications or additional documents, the investigator should inform the IRB of any new information (e.g., new information about risks of the research interventions) the investigator has become aware of since the convened IRB meeting that might alter the IRB's determinations under 45 CFR 46.111 and, if applicable, subparts B, C, and D of 45 CFR part 46.

3. Determining the Date for the *Second and all Subsequent Continuing Reviews for Research Reviewed by the IRB at Convened Meetings and Approved for One Year Intervals, Including How to Maintain a Fixed Anniversary Date for the Expiration of Annual IRB Approvals*

An IRB must conduct continuing review of research at intervals appropriate to the degree of risk, but not less than once per year (45 CFR 46.109(e)). Given this requirement, it is important to

recognize that the use of the “effective date” of IRB approval – as opposed to the date of the convened meeting at which the IRB approved a research study with conditions as described in the section G.2 above – to determine the continuing review date in general *only applies to the first continuing review*. For all subsequent continuing reviews of a research study, since there will be an on-going approved study, the date of the convened meeting when the IRB conducts continuing review and approves the study (with or without conditions) determines the date of the next continuing review.

OHRP recognizes the logistical advantages of keeping the expiration date of the IRB approval period constant from year to year throughout the life of a research project. Therefore, when (a) the IRB grants approval for one year at the time of each continuing review, and (b) the IRB performs continuing review and re-approves (with or without conditions) the research within 30 days *before* the IRB approval period expires, the IRB may retain the anniversary of the expiration date of the initial IRB approval as the expiration date of each subsequent one-year approval period. For example, if an IRB conducts initial review of a research project and approves it without conditions on October 1, 2009 for one year, the IRB may conduct its first continuing review anytime between September 1 and October 1, 2010, and re-approve the research for another one-year period that expires on October 1, 2011. The same timing may be applied to each subsequent continuing review until the research activities involving human subjects are completed. Institutions that adopt a procedure for maintaining fixed anniversary dates for the expiration of annual IRB approvals should include a description of this procedure in their written IRB procedures (see section C.3 for additional guidance on written IRB procedures for conducting continuing review).

Determining the dates for continuing reviews after the first continuing review should be straightforward. The following scenarios provide further clarification regarding how to implement this guidance in circumstances where the IRB approves research at the time of continuing review at a convened meeting either with or without conditions:

- Scenario A: An IRB conducts initial review of a research project at a convened meeting and approves it without conditions on October 1, 2009 for one year. The effective date of the initial IRB approval is October 1, 2009, and that approval expires on October 1, 2010. The IRB follows a procedure for maintaining fixed anniversary dates for the expiration of annual IRB approvals and conducts its first continuing review of the research project at a convened meeting on September 15, 2010 and re-approves the project without conditions for another one-year period. The expiration date of the second approval period is October 1, 2011. The second continuing review must occur by October 1, 2011.
- Scenario B: Same facts as scenario A, except that the IRB does not follow a procedure for maintaining fixed anniversary dates for the expiration of annual IRB approvals. The expiration date of the second approval period is September 15, 2011, and the second continuing review must occur by this date.
- Scenario C: Same facts as scenario A, except that the IRB conducts its first continuing review of the research project at a convened meeting on August 15, 2010 and re-approves the project without conditions for another one-year period. Because the first continuing review did not occur within 30 days before the IRB approval period expired, the

expiration date of the second approval period is August 15, 2011, and the second continuing review must occur by this date.

- Scenario D: Same facts as scenario A, except that when the IRB conducts its first continuing review on September 15, 2010, it re-approves the research for another one-year period with the condition that the investigator makes a change to the protocol. On September 22, 2010, the IRB chairperson receives from the investigator a revised protocol, and verifies that the required change has been made. The expiration date of the second approval period is October 1, 2011, and the second continuing review must occur by this date.
- Scenario E: Same facts as scenario D, except that that the IRB does not follow a procedure for maintaining fixed anniversary dates for the expiration of annual IRB approvals. The expiration date of the second approval period is September 15, 2011, and the second continuing review must occur by this date.
- Scenario F: Same facts as scenario A, except that when the IRB conducts its first continuing review on September 15, 2010, it re-approves the research for another one-year period with the condition that the investigator makes a change to the informed consent document within 60 days. The IRB directs the IRB chairperson to review, on behalf of the IRB, the revised informed consent document and determine whether the changes required by the IRB have been made. The IRB also specifies that no new subjects may be enrolled in the research until the IRB chairperson reviews the revised informed consent document and verifies that the required change has been made. On October 31, 2010, the IRB chairperson reviews the revised informed consent document and determines that the changes made by the investigator are satisfactory. Enrollment of new subjects may resume on October 31, 2010. The expiration date of the second approval period is October 1, 2011, and the second continuing review must occur by this date.
- Scenario G: An IRB conducts initial review of a research project at a convened meeting and approves it without conditions on October 1, 2009 for one year. The effective date of the initial IRB approval is October 1, 2009, and that approval expires on October 1, 2010. The investigator does not submit the necessary progress report for the first continuing review until October 31, 2010. As a result, IRB approval expired on October 1, 2010, and all research activities involving human subjects must stop except in the limited circumstances described in section H below. The IRB conducts its first continuing review of the research project at a convened meeting on November 15, 2010 and re-approves the project without conditions for another one-year period. The expiration date of the second approval period is November 15, 2011, and the second continuing review must occur by this date.

4. Determining the Continuing Review Date for Research Reviewed by the IRB at a Convened Meeting and Approved for Less Than One Year

As discussed in section F above, the IRB may determine that a research project must undergo continuing review more often than annually. The same guidelines for determining the continuing review dates as discussed in sections G.2 and G.3 above would apply in such circumstances, as demonstrated in the following examples:

- An IRB conducts initial review of a research project at a convened meeting on October 1, 2009 and approves the project for 6 months without requiring (a) any changes to the protocol or informed consent document(s), or (b) submission of any clarifications or additional documents. The effective date of the initial IRB approval is October 1, 2009, and the first continuing review must occur within six months of the date of the IRB meeting, that is, by April 1, 2010. The IRB conducts its first continuing review of the research project at a convened meeting on March 15, 2010 and re-approves the project without conditions for another six-month period. The IRB stipulates that the expiration date of the second approval period is October 1, 2010, and the second continuing review must occur by this date.
- An IRB conducts initial review of a research project at a convened meeting on October 1, 2009, approves the project for 6 months, and requires that the investigator make minor changes to the protocol as a condition of its approval. The IRB directs the IRB chairperson to review, on behalf of the IRB, the revised protocol and determine whether the changes required by the IRB have been made. On November 1, 2009, the IRB chairperson reviews the revised protocol and determines that the changes made by the investigator are satisfactory. The effective date of the initial IRB approval is November 1, 2009, and the first continuing review must occur within six months of that date, that is, by May 1, 2010. The IRB follows a procedure for maintaining fixed anniversary dates for the expiration of annual IRB approvals, and conducts its first continuing review of the research project at a convened meeting on April 15, 2010 and re-approves the project without conditions for one year. The expiration date of the second approval period is May 1, 2011, and the second continuing review must occur by this date.
- At a convened meeting on October 1, 2009, an IRB conducts initial review of a research project that is a high-risk phase I clinical trial involving healthy subjects and approves the project for 6 months or until the first three subjects have enrolled and received the study intervention – whichever is sooner – without requiring (a) any changes to the protocol or informed consent document(s), or (b) submission of any clarifications or additional documents. The effective date of the initial IRB approval is October 1, 2009, and the first continuing review must occur within six months of the date of the IRB meeting, that is, by April 1, 2010, or after the first three subjects have enrolled and received the study intervention, whichever is sooner. The third subject is enrolled and receives the study intervention on February 1, 2010. No further subjects can be enrolled in the project until the IRB conducts continuing review at a convened meeting and re-approves the research. The IRB conducts its first continuing review of the research project at a convened meeting on February 15, 2010 and re-approves the project without conditions for another six-month period or until the next three subjects have enrolled and received the study intervention – whichever is sooner. The next continuing review must occur by August 15, 2010, or after the next three subjects have enrolled and received the study intervention, whichever is sooner.

5. Determining the Continuing Review Date for Research Reviewed by the IRB Under an Expedited Review Procedure

For a research project approved at the time of initial review under an expedited review procedure, continuing review must occur within 1 year of the effective date of the initial approval by the IRB chairperson or IRB member(s) designated by the chairperson (45 CFR 46.109(e)). Again, the same guidelines for determining the continuing review dates as discussed in sections G.2 and G.3 above would apply in such circumstances, as demonstrated in the following examples:

- An IRB chairperson conducts initial review of a research project under an expedited review procedure on October 1, 2009 and approves the project for one year without requiring (a) any changes to the protocol or informed consent document, or (b) submission of any clarifications or additional documents. The effective date of the initial IRB approval is October 1, 2009, and the first continuing review must occur within one year of that date, that is, by October 1, 2010. The IRB follows a procedure for maintaining fixed anniversary dates for the expiration of annual IRB approvals, and the IRB chairperson conducts the first continuing review of the research project under an expedited review procedure on September 15, 2010 and re-approves the project without conditions for one year. The expiration date of the second approval period is October 1, 2011, and the second continuing review must occur by this date.
- An IRB chairperson conducts initial review of a research project under an expedited review procedure on October 1, 2009, approves the project for one year, and requires that the investigator make minor changes to the protocol as a condition of the IRB's approval. On November 1, 2009, the IRB chairperson reviews the revised protocol and determines that the changes made by the investigator are satisfactory. The date of the initial IRB approval is November 1, 2009, and the first continuing review must occur within one year of that date, that is, by November 1, 2010. The IRB does not follow a procedure for maintaining fixed anniversary dates for the expiration of annual IRB approvals, and the IRB chairperson conducts the first continuing review under an expedited review procedure on October 15, 2010, and re-approves the research for another one-year period with the condition that the investigator makes a specific word change to the informed consent document. The IRB chairperson designates the IRB administrator, who is not an IRB member, to review the revised informed consent document and confirm that the required change was made. On October 22, 2010, the IRB administrator receives from the investigator a revised informed consent document, and verifies that the required change has been made. The expiration date of the second approval period is October 15, 2011, and the second continuing review must occur by this date.

H. Lapses in IRB Approval

As previously noted, continuing review of research must occur at intervals appropriate to the degree of risk, but not less frequently than once per year (45 CFR 46.109(e)). OHRP recommends that the IRB establish written procedures for informing investigators of the HHS regulations at 45 CFR part 46 and the IRB's own policies and procedures on continuing review

requirements. This applies whether the research projects are reviewed by the IRB at a convened meeting or under an expedited review procedure.

OHRP recommends that the IRB and the investigator plan ahead to ensure that continuing review and re-approval of research occurs prior to the end of the approval periods specified by the IRB. OHRP further recommends that the IRB's written procedures provide for sufficient advance notice to the investigator to ensure that the requirements for continuing review are met by the date on which approval would expire. The IRB should develop administrative procedures, such as computerized tracking systems, to minimize any unintended expiration of IRB approval. OHRP cautions, however, that if investigators submit materials for continuing review too far in advance of the expiration date of IRB approval, the materials may no longer be relevant by the time that continuing review actually takes place. Therefore, OHRP recommends that the IRB work to link as closely in time as possible:

- The receipt by the IRB of continuing review materials;
- The review of those materials by the IRB; and
- The impending expiration date for IRB approval.

The HHS regulations at 45 CFR part 46 make no provision for any grace period extending the conduct of research beyond the expiration date of IRB approval. If an investigator has failed to provide continuing review information to the IRB or the IRB has not conducted continuing review and re-approved a research project by the expiration date, all research activities involving human subjects must stop, *unless* it is determined to be in the best interests of already enrolled subjects to continue participating in the research. Enrollment of new subjects cannot occur after the expiration of IRB approval. Continuing participation of already enrolled subjects in a research project during the period when IRB approval has lapsed may be appropriate, for example, when the research interventions hold out the prospect of direct benefit to the subjects or when withholding those interventions poses increased risk to the subjects (see section J below for additional guidance).

The determination regarding whether it is in the best interests of already enrolled subjects to continue to participate in the research after IRB approval has expired may be made initially by the investigator, but the investigator should seek confirmation that the IRB agrees with this determination as soon as possible. Furthermore, this determination may be made for all enrolled subjects as a group or for each individual subject. If the investigator or IRB determines that it is not in the best interests of already enrolled subjects to continue to participate, investigators must stop all human subjects research activities, including intervening or interacting with subjects and obtaining or analyzing identifiable private information about human subjects (45 CFR 46.109(a) and (e)).

When IRB approval of an ongoing research project lapses, the IRB should complete continuing review for the project as soon as possible. Investigators may resume the human subjects research activity once continuing review and approval by the IRB has occurred. OHRP recommends that the IRB document why the lapse in IRB approval occurred, and the steps that the IRB is taking to prevent any such lapse of approval of the project from occurring again in the future.

Furthermore, when IRB approval of an ongoing research project lapses and the IRB subsequently re-approves the project for one year, a new anniversary date for the expiration date of subsequent approval periods will be established (see scenario F in section G.2 above).

When continuing review of a research project does not occur prior to the end of the approval period specified by the IRB, IRB approval expires automatically. OHRP does not consider such an expiration of IRB approval to be a suspension or termination of IRB approval. Therefore, such expirations of IRB approval do not need to be reported to OHRP under the HHS regulations at 45 CFR 46.103(b)(5).

I. Communicating the IRB's Continuing Review Determination to Investigators and the Institution

The IRB must notify the investigator and the institution in writing of its decision to approve or disapprove proposed research, or of modifications required to secure IRB approval of the research (45 CFR 46.103(b)(4) and 46.109(d)). Furthermore, if the IRB decides to disapprove research, it must include in its written notification a statement of the reasons for its decision and give the investigator an opportunity to respond in person or in writing (45 CFR 46.109(d)). These notification requirements apply to both initial and continuing review. Therefore, after an IRB completes its continuing review of a research project, the IRB must provide written notification informing the investigator of the IRB's determination (e.g., approval, requiring modification(s) to secure approval, or disapproval).

For research projects that are approved to continue, the IRB's notification to the investigator must clearly state the period of time for which the project is approved, any conditions of the IRB's approval, and the date by which the next continuing review must occur (45 CFR 46.103(b)(4) and 46.109(d))(see section G above for additional guidance on how to determine the effective date of initial IRB approval and continuing review dates). OHRP also recommends that written IRB procedures related to continuing review describe which institutional office(s) and official(s) are notified of IRB findings and actions regarding continuing review and how notification to each is accomplished.

J. Suspension or Termination of IRB Approval of Research or Disapproval of Research at the Time of Continuing Review

The IRB has the authority to suspend or terminate approval of research that is not being conducted in accordance with the IRB's requirements or that is associated with unexpected serious harm to subjects (45 CFR 46.113). A suspension or termination of IRB approval of research may occur at anytime during the period for which IRB approval had already been given.

Suspension of IRB approval may be appropriate when a significant issue is first identified and while the IRB investigates the matter. For example, if there is an allegation of serious noncompliance by an investigator or a human subject safety issue that needs further investigation and evaluation, the IRB may decide to suspend its approval of the research project while the allegation or issue is undergoing evaluation. In addition, the IRB may consider whether it is

appropriate to notify subjects about the suspension and the reasons for it, and if so, when the subjects should be notified, given that complete information may not be available.

Any suspension or termination of IRB approval must be promptly reported to the investigator, appropriate institutional officials, the HHS agency that supported the research, and OHRP (45 CFR 46.103(b)(5) and 46.113). Such reports must include the reasons for the IRB's action (45 CFR 46.113).

IRBs must follow written procedures for ensuring such reporting (45 CFR 46.108(a)). When reporting the suspension or termination of IRB approval of a research project to OHRP, OHRP recommends that the report include the following information:

- The name of the institution(s) (e.g., university, hospital, foundation, school, etc) conducting the research project;
- The title of the research project and the title of any related grant, contract, or cooperative agreement;
- The name of the principal investigator for the research project;
- The number of the research project assigned by the IRB and the number of the applicable HHS award(s) (grant, contract, or cooperative agreement);
- A detailed description of the reason for the suspension or termination; and
- The actions the institution is taking or plans to take to address the suspension or termination (e.g., investigate alleged noncompliance, educate the investigator, educate all research staff, require monitoring of the investigator or the research project, etc.)

When an IRB (a) suspends or terminates its approval during the period for which IRB approval had already been given or (b) disapproves a research project at the time of continuing review, the IRB should establish procedures to ensure that the rights and welfare of currently enrolled subjects are protected, subjects are not put at risk, and subjects receive appropriate care, if indicated, during the period of suspension or following the cessation of the research. This is particularly important in the context of clinical trials. For example, the IRB may need to determine whether currently enrolled subjects should (a) continue receiving the interventions that were being administered to subjects under the research project, (b) be transferred to another institution engaged in the research so that participation of the subjects in the research may continue, or (c) be transitioned to medical management outside of the research context. Continuation of subjects on interventions that were being administered under the research project may be appropriate at least temporarily, for example, when those interventions hold out the prospect of direct benefit to the subjects or when withholding those interventions poses increased risk to the subjects. If the IRB decides that already enrolled subjects should continue to receive the interventions that were being administered to subjects under the research project, data collection (especially safety information) should also continue for such subjects.

K. Identifying the Point When Continuing Review is no Longer Necessary

Continuing review and re-approval of a research project at least annually is required so long as the project continues to involve human subjects. OHRP considers a research project to continue to involve human subjects as long as the investigators conducting the research continue to obtain:

- Data about the subjects of the research through intervention or interaction with them; or
- Identifiable private information about the subjects of the research.

With respect to *obtaining identifiable private information*, OHRP considers this to include obtaining identifiable biological specimens originating from living individuals. Furthermore, OHRP considers *obtaining identifiable private information* to include:

- Collecting or receiving identifiable private information (including identifiable biological specimens) from any source (i.e., not already in the possession of the investigator);
- Collecting identifiable private information by observing or recording private behavior without interacting or intervening with the human subjects; and
- Using, studying, or analyzing identifiable private information (including identifiable biological specimens), even if the information was already in the possession of the investigator before the research begins. This includes using, studying, or analyzing any of the following:
 - Identifiable private information obtained by interacting or intervening with the human subjects;
 - Identifiable private information stored in documents, records, photographs, images, video recordings, or audio recordings provided to the investigators from any source;
 - Identifiable private information stored in documents, records, photographs, images, video recordings, or audio recordings already in the possession of the investigator before the research begins;
 - Identifiable private information obtained about an individual by interviewing other people (e.g., an individual's healthcare provider or teacher);
 - Identifiable biological specimens provided to the investigators from any source; or
 - Identifiable biological specimens already in the possession of the investigator before the research begins.

A research project no longer involves human subjects once the investigators have finished obtaining data through interaction or intervention with subjects or obtaining identifiable private information about the subjects, which includes the using, studying, or analyzing identifiable private information. Once all such activities described in the IRB-approved protocol are finished, the research project no longer needs to undergo continuing review. For example, when the only remaining activity of a research project involves the analysis of aggregate data sets without individual subject identifiers, no further continuing review is necessary. At that point the IRB can formally close the IRB file for that project and advise the investigator of that action.

See section D.1 above for additional guidance on determining when continuing review is no longer required for a particular institution involved in the conduct of a multicenter research project.

L. Continuing Review is not Required for Exempt Human Subjects Research Projects

Human subjects research studies that qualify for exemption under 45 CFR 46.101(b) are exempt from all requirements of 45 CFR part 46, including the requirements related to continuing review. Investigators should follow the established institutional policies and procedures for determining whether proposed human subjects research projects are exempt. Once the determination has been made that a project is exempt, no continuing review of the project by the IRB is required under the HHS regulations at 45 CFR part 46.

However, if an investigator decides to modify an exempt human subjects research project in such a way that it would no longer qualify for exemption, the investigator must submit the modified research protocol to the IRB for review prior to implementation of the modified research project (45 CFR 46.103(b) and 46.109(a)).

If you have specific questions about how to apply this guidance, please contact OHRP by phone at (866) 447-4777 (toll-free within the U.S.) or (240) 453-6900, or by e-mail at ohrp@hhs.gov.