Guidance for IRBs, Clinical Investigators, and Sponsors

IRB Continuing Review after Clinical Investigation Approval

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)
Center for Drug Evaluation and Research (CDER)
Office of Good Clinical Practice (OGCP)

February 2012
Procedural

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Contains Nonbinding Recommendations

Guidance for IRBs, Clinical Investigators, and Sponsors[1] IRB Continuing Review after Clinical Investigation Approval

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance is intended to assist institutional review boards (IRBs) in carrying out their continuing review responsibility under 21 CFR 56.108(a) and 56.109(f) by providing recommendations regarding the criteria, process, and frequency of continuing review to assure the protection of the rights and welfare of human subjects enrolled in clinical investigations. This guidance should also help clinical investigators and sponsors better understand their responsibilities related to continuing review. This document supersedes the Information Sheet, *Continuing Review After Study Approval* (September 1998, Office of Health Affairs, FDA). To enhance human subject protection and reduce regulatory burden, the Department of Health and Human Services (HHS), Office for Human Research Protections (OHRP) and FDA have been actively working to harmonize the agencies' regulatory requirements and guidance for human subject research. This guidance document was developed as a part of these efforts.[2]

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word "should" in Agency guidances means that something is suggested or recommended, but not required.

[1] This guidance has been prepared by FDA's Institutional Review Board Working Group, which includes representatives from FDA's Office of the Commissioner, Center for Biologics Evaluation and Research (CBER), Center for Drug Evaluation and Research (CDER), and Center for Devices and Radiological Health (CDRH).

[2] For studies subject to 45 CFR part 46 (i.e., studies that are funded, conducted, or supported by HHS, OHRP has issued guidance on IRB continuing review. See "Guidance on IRB Continuing Review of Research," http://www.hhs.gov/ohrp/policy/continuingreview2010.pdf and "Guidance on IRB Approval of Research with Conditions," http://www.hhs.gov/ohrp/policy/conditionalapproval2010.html.

II. BACKGROUND

FDA's IRB regulations were first issued in 1981, when the single investigator-single site study was the norm for clinical trials, 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 a study. Since that time, multi-site studies have become commonplace. Although an individual investigator informs the IRB about events at the investigator's site, the investigator and IRB may not generally be well-informed about the far greater body of data reflecting events across all study sites. IRB review and oversight of such research has consequently become more challenging. Given the changes in the way clinical studies are conducted, this guidance makes specific recommendations to assist IRBs in conducting continuing review.

III. DISCUSSION

With respect to continuing review, FDA's regulations require an IRB to develop and follow written procedures for:

- Conducting continuing review of research at intervals appropriate to the degree of risk, but not less than once a year (21 CFR 56.108(a)(1) and 56.109(f));

- Determining which clinical investigations require review more often than annually (21 CFR 56.108(a)(2));

- Determining which clinical investigations need verification from sources other than the clinical investigator that no material changes in the research have occurred since the previous IRB review (21 CFR 56.108(a)(2)); and

- Ensuring prompt reporting to the IRB of changes in 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 where necessary to eliminate apparent immediate hazards to the human subjects (21 CFR 56.108(a)(3) and (4)).

The purpose of written procedures is to ensure that IRBs have a framework for periodically reviewing the conduct of clinical investigations of FDA-regulated products (e.g., drugs, including biologics, and devices). FDA's regulations do not provide specific instructions to IRBs on how to set up their own rules. The regulations allow institutions and IRBs to develop their own procedures or additional requirements as appropriate to the IRB's needs.

While a clinical investigation is ongoing, IRBs review and consider changes in research as they are received, including protocol amendments.[3] They also review changes to the informed consent document,[4] reports from investigators or sponsors of unanticipated problems,[5] and other

[3] See 21 CFR 56.108(a)(3) and (4), 56.109(a), and 56.110(b)(2).
[4] See 21 CFR 56.109(b).
[5] See 21 CFR 56.108(b)(1).

information about the investigation. IRB review of a proposed change in research during the period for which approval is authorized does not constitute continuing review of the research 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). Although an IRB may become familiar with various individual aspects of the study's conduct, such familiarity does not relieve the IRB of the responsibility to conduct continuing review, which provides an opportunity to reassess the totality of the study and assure that, among other things, risks to subjects are (1) minimized, and (2) still reasonable in relation to anticipated benefits, if any, to subjects and the importance of the knowledge that may be expected to result (21 CFR 56.111(a)(1) and (2)).

This formal review of the research effort, as required under 21 CFR 56.109(f), is the subject of this guidance. An IRB must review previously approved research at least once a year (21 CFR 56.109(f)). Review must be conducted 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, unless the research qualifies for review through an expedited process (21 CFR 56.108(c) and 56.110). See Section III.D. of this guidance for more information on the application of expedited review procedures to continuing review.

IRBs involved in multi-site studies may find it difficult to conduct a thorough review with data solely from the site(s) under their purview and may need to obtain study-wide information. Sponsors are in the unique position of having information for the entire study[6] and may provide it to investigators, who in turn provide it to the IRBs. FDA's regulations do not prohibit sponsors from providing study-wide information directly to IRBs.[7] FDA encourages efforts by investigators and sponsors to ensure that IRBs receive meaningful study-wide information, particularly when doing so may assist IRBs in reviewing the studies and protecting subjects.

One way to enable a useful continuing review of multi-site studies while reducing or eliminating duplication of effort is through the use of cooperative review agreements or other mechanisms (e.g., using a centralized IRB review process), in accordance with 21 CFR 56.114. Cooperative agreements may vary with respect to how continuing review will be carried out. For example, some agreements may designate a specific IRB as having primary responsibility for continuing review of an investigation.[8] Other agreements may assign responsibility for local issues to the institution's IRB, but assign the remaining aspects of continuing review to a central IRB.

Whatever the arrangement, the IRB(s) responsible for continuing review of multi-site studies may find it helpful to obtain and review information across the entire study. For additional discussion, see Section III.B. of this guidance.

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[6] See FDA's Guidance for Industry, "Adverse Event Reporting to IRBs – Improving Human Subject Protection," http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126572.pdf.

[7] Note that FDA's regulations for device studies specifically assign general responsibility to sponsors "…for ensuring IRB review and approval are obtained and ensuring that any reviewing IRB and FDA are promptly informed of significant new information about an investigation…" 21 CFR 812.40.

[8] See FDA's Guidance for Industry, "Using a Centralized IRB Review Process in Multicenter Clinical Trials," http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm080606.pdf.

A. Criteria for Approving Research During Continuing Review

FDA regulations set forth the criteria for IRB approval of research (21 CFR 56.111). These criteria apply to both initial review and continuing review. In order to approve research, the IRB must determine that all of following requirements are satisfied:

- Risks to subjects are minimized;
- Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may be expected to result;
- Selection of subjects is equitable;
- Informed consent will be sought from each prospective subject or the subject's legally authorized representative, and appropriately documented;
- Where appropriate, the research plan adequately provides for monitoring the data collected to ensure the safety of subjects;
- Where appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data;
- Appropriate additional safeguards are included to protect vulnerable subjects; and
- Where the study involves children, the research complies with 21 CFR part 50, Subpart D.

The IRB makes its continuing review determination by considering whether any new information is available that would affect the IRB's prior finding that the research meets the criteria in 21 CFR 56.111. IRBs have authority to disapprove or require modifications in (to secure re-approval of) a research activity that does not meet any of the above criteria (e.g., the full study or any part thereof, such as changes to the protocol, advertisements; 21 CFR 56.109(a))

B. Process for Conducting Continuing Review

Continuing review takes place at a convened meeting of the IRB, unless it meets the criteria for expedited review under 21 CFR 56.110. (See 21 CFR 56.108(c) and Section III.D. of this guidance.) The IRB is required to review the research (21 CFR 56.109(f)) and must maintain records of its continuing review activities, including minutes of meetings at which such activities are undertaken (21 CFR 56.115(a)(2) and (3)). The minutes must be in sufficient detail to show actions taken by the IRB, and the vote on these actions, and to summarize the discussion of controverted issues and their resolution (21 CFR 56.115(a)(2)). For research to be approved, a majority of IRB members present at a meeting must approve it (21 CFR 56.108(c)).

The IRB must ensure that a member does not 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 (21 CFR 56.107(e)). Meeting minutes must reflect meeting attendance, the votes taken, and a summary of the discussion and resolution of controverted issues, and should provide confirmation that conflicted members did not participate in the IRB's continuing review of their studies (21 CFR 56.115((a)(2)). FDA recommends that IRB members with a conflicting interest in a project recuse themselves by leaving the meeting room when the IRB conducts continuing review of that project, except when requested by the IRB to be present to provide information.

This IRB member recusal should be noted in the minutes of the IRB meeting when recording votes on IRB actions.

An IRB must maintain and follow written procedures for the continuing review of research (21 CFR 56.108(a)(1) and 56.115(a)(6)). In developing procedures for continuing review, the IRB should consider the use of templates, checklists, or other tools to standardize the request for information or list of materials to be provided to the IRB at the time of continuing review.

Investigators are responsible for ensuring that studies they conduct comply with applicable regulatory requirements.[9] To ensure that the reviewing IRB can carry out its review prior to the expiration date of the current IRB approval, investigators should follow the IRB's policies and procedures for continuing IRB review of research (procedures required by 21 CFR 56.108(a)(1)), in particular by submitting materials and information required by the IRB. FDA encourages IRBs to make investigators aware of the IRB's procedures, for example, by enclosing a copy in correspondence informing the investigator of the IRB's decisions, or posting the information on a website.

FDA recommends that the IRB's written procedures call for submission of the following information for consideration by the IRB in continuing review, if not already available to the IRB as part of the existing IRB records for the research[10]:

- A written progress report/brief project summary that includes the following or references other documents made available to the IRB:
    - The number of subjects accrued; (For multi-site studies, the number of subjects accrued at the local site and the number accrued study-wide, if available, should be provided.)
    - 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 FDA does not expect the IRB to perform an independent review of the relevant scientific literature related to a particular research project undergoing continuing review.)
    - A summary of any unanticipated problems.[11] In many cases, such a summary could be a brief statement that there have been no unanticipated problems (i.e., 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));

[9] See 21 CFR 312.53(c)(1)(vii), 312.60, 312.66, 812.36(c)(viii), 812.100, 812.110(b), 812.40, and 812.43(c)(4)(i).
[10] Some of this information may come from the sponsor, who would have access to data across all study sites. Sponsors may provide information directly to IRBs or to the clinical investigators who in turn would share it with the IRBs.
[11] IRB procedures must ensure that there is prompt reporting to the IRB of unanticipated problems involving risks to human subjects or others (21 CFR 56.108(b)(1)). See "Guidance for Clinical Investigators, Sponsors, and IRBs: Adverse Event Reporting to IRBs--Improving Human Subject Protection," http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126572.pdf.

  - A summary of any subject withdrawals 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 enrolled at the local site since the last IRB review;
- The latest version of the protocol and sample informed consent document(s) in use at the site;
- Any proposed modifications to the informed consent document or protocol;
- The current Investigator's Brochure, if any, including any modifications;
- Any other significant information related to subject risks, such as the most recent report, if any, from data monitoring committees (DMCs);[12] (Additionally, it may be useful for sponsors to ensure that IRBs are informed when DMCs have met, even when no problems have been identified and the DMC has recommended continuation of the study as designed. This information can be transmitted either by the investigator or directly by the sponsor.) and
- Aggregate information about relevant regulatory actions occurring since the last review that could affect safety and risk assessments (e.g., withdrawal or suspension from marketing in any country on the basis of safety, reports of recalls and device disposition required by 21 CFR 812.150(b)(6)).

If the information listed above is not already included in an existing report (prepared by the sponsor for some other purpose or entity),[13] then a separate progress report should be prepared and submitted to the IRB for continuing review of the study. However, if the information listed above is included in an existing report then this report may be re-purposed and submitted to the IRB at the time of continuing review of the study. For example, as noted above, sponsors of investigational drug studies are required by 21 CFR 312.33 to submit annual reports to FDA on the progress of their studies. Sponsors of investigational device studies are already required to provide progress reports to all reviewing IRBs at least annually (21 CFR 812.150(b)(5)).

Submitting the annual report for drug studies or the progress report for device studies is one mechanism of providing the IRB with pertinent information for consideration at the time of continuing review. These reports, with little or no modification, usually will contain the information listed above, and could be redacted such that proprietary information and information about other studies unrelated to the continuing review are removed prior to submission to the IRB.

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[12] See FDA's "Guidance for Clinical Trial Sponsors, Establishment and Operation of Clinical Trial Data Monitoring Committees," http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm127073.pdf .

[13] FDA received comments that international regulatory authorities require periodic aggregate reports be submitted to independent ethics committees (IECs). Because these reports are already being generated and are written for IRBs/IECs for global research, it was suggested that these reports could be used as a means of reducing burdens and harmonizing requirements for multinational trials, while providing necessary information to IRBs. [See Docket # FDA-2009-D-0605, accessible on www.regulations.gov .] FDA does not object to this practice. For clinical investigations involving drugs and biologics, IRBs could ask for the Development Safety Update Report (DSUR) Executive Summary, if available. The main objective of a DSUR is to present a comprehensive, thoughtful annual review and evaluation of pertinent safety information collected during the reporting period related to a drug under investigation, whether or not it has a marketing approval. See ICH "Guidance for Industry, E2F Development Safety Update Report," http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073109.pdf .

When an IRB is conducting continuing review, the IRB should be knowledgeable about the investigation, including materials associated with previous ad hoc or scheduled reviews related to protocol amendments, the Investigator's Brochure, or unanticipated problems involving risks to subjects. The IRB file, including relevant IRB meeting minutes, should be made available to IRB members prior to the meeting at which continuing review will be conducted. The file should also be accessible during the meeting at which the research is discussed to allow members to resolve any questions that may arise.

For multi-site studies, IRBs should obtain study-wide information, DMC reports, and any other information about the test article that would be relevant to the IRB's continuing review. The investigator can provide this information to the IRB, but may first need to obtain the information from the sponsor. The investigator and sponsor can agree that the sponsor will submit this information directly to the IRB. Sponsors are in the unique position of having information across all study sites, interim assessments by DMCs, and safety information obtained or otherwise received from any source, foreign or domestic (e.g., information derived from any clinical or epidemiological investigations, animal investigations, commercial marketing experience, relevant articles from published or unpublished sources, reports from non-U.S. regulatory authorities), that could assist the IRB in reviewing the study and protecting subjects.[14]

The IRB that conducted the initial review of a study may be best suited to conduct continuing review of the study because of its familiarity with the study and/or previous review(s). However, FDA is aware that some institutions have designated one or more IRBs for the sole purpose of conducting continuing review. It is permissible under FDA regulations for an IRB other than the IRB that conducted the initial review to perform continuing review of a study, as long as the IRB conducting the continuing review satisfies regulatory requirements such as the IRB membership requirements under 21 CFR 56.107 and fulfills the regulatory requirements for conducting continuing review. The IRB conducting continuing review should also have access to all prior relevant IRB records.

FDA recommends that, whenever possible, an IRB's written procedures include measures intended to reduce burdens and allow the IRB to efficiently accomplish its continuing review workload. For example, IRB written procedures may allow:

- appropriately trained staff to perform preliminary review of study materials to assure that the documents necessary for continuing review have been submitted and the file is complete; and
- one or more experienced IRB members to perform primary review of the continuing review file and report, summarize changes or critical issues for the other members, and lead the discussion at a convened meeting (e.g., "no/only minimal changes since the last continuing review date"; "AE reports are of the type and frequency as described in the current Investigator's Brochure or informed consent document; no changes are necessary at this time").

[14] See "Guidance for Clinical Investigators, Sponsors, and IRBs: Adverse Event Reporting to IRBs--Improving Human Subject Protection," http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126572.pdf .

FDA is aware of instances in which an IRB has allowed voting on groups of studies (sometimes called "block voting"). If block voting is to be used, FDA recommends that the IRB's procedures provide IRB members with ample opportunity to carefully consider and discuss studies individually and express concerns before the voting occurs. The IRB's procedures should allow members to vote "yes" on some studies, "no" on others, and abstain on others.

C. Key Topics to Consider During Continuing Review

When conducting continuing review, the IRB should start with the assumption that the research, as previously approved, satisfied all of the criteria under 21 CFR 56.111. The IRB should focus on any new information provided by the investigator or sponsor, or otherwise available to the IRB, that may 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. If the IRB determines that a research activity no longer meets the criteria for approval under 21 CFR 56.111, the IRB is not permitted to reapprove it, but may either disapprove it or require modifications in order to secure re-approval (21 CFR 56.109(a)).

As discussed below, 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 areas: 1) Risk Assessment; 2) Adequacy of Informed Consent; 3) Local Issues, and 4) Trial Progress.

The amount of time the IRB spends on the continuing review of a particular study will vary depending on the nature and complexity of the research, the amount and type of new information presented to the IRB and whether the investigator is seeking approval of substantive changes to the research protocol or informed consent document. For many studies, continuing review can be fairly straightforward, and the IRB should be able to complete its deliberations and review promptly.

1. Risk Assessment

During continuing review, the IRB must determine that the criteria necessary for IRB approval under 21 CFR 56.111 are met. This includes determining whether information provided at the time of continuing review would alter either the conclusion 1) that the risks to subjects are minimized, or 2) that the risks to subjects are reasonable in relation to anticipated benefits (21 CFR 56.111(a)(1) and (2)). The IRB's review procedures under 21 CFR 56.108 should ensure that the IRB will consider any new information that has been received since the date that the IRB last reviewed the study (e.g., sponsor's annual report, periodic aggregate reports, any analysis by the sponsor performed since then). See Section III.B. of this guidance.

2. Adequacy of Informed Consent

At the time of continuing review, the IRB should review the informed consent document to verify that the site is using the most recently approved version, and evaluate whether this document contains accurate, up-to-date information about the study. FDA recommends use of

methods that will allow the IRB to readily recognize the most current version of the informed consent document, for example, using date stamps or initialing and dating documents to indicate when a version was approved.

When reviewing informed consent document(s), the IRB must evaluate whether the currently approved consent document or any revised consent document proposed for approval contains accurate, up-to-date information about the study (i.e., meets the criteria in 21 CFR 50.25, including the requirement to include any reasonably foreseeable risks. See 21 CFR 56.109(b) and 56.111(a)(4-5)). In particular, the IRB's continuing review may reveal new risk information that will require updating of informed consent materials in order to satisfy these requirements. Although the IRB may have reviewed the informed consent document when new information or a protocol amendment was submitted to the IRB, such review would not eliminate the need to review the informed consent document during continuing review. In addition, the IRB should ensure that information about any significant new findings identified since the last continuing review that may relate to the subjects' willingness to continue participation will be provided to enrolled subjects (e.g., important toxicity information, or adverse event information identified during analysis of reports across all sites).

In multi-site studies, a central IRB may be reviewing the adequacy of informed consent, depending on the agreement between the local IRB and the central IRB. The central IRB may accomplish this function by reviewing a model/template informed consent document or site-specific informed consent documents in use at one or more, or even all, individual sites.[15]

3. Local Issues

The reviewing IRB should consider local concerns during both initial and continuing review, including:

- Changes in the investigator's situation or qualifications (e.g., suspension of hospital privileges, medical license; involvement in numerous clinical trials);
- Evaluation, investigation, and resolution of complaints related to 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 regulations, applicable state and local law, or standards of professional conduct or practice;
- Reports from third party observation of the research (including the informed consent process) carried out under 21 CFR 56.109(f); and
- Investigator concerns about trial conduct at the local site (e.g., study coordinator ineffectiveness, inability of subjects to understand sections of the informed consent document required by institutional policies).

If review responsibilities for a study are shared under a cooperative agreement, the written agreement should identify the responsibilities covered by the agreement and who is responsible

[15] See "Guidance for Industry: Using a Centralized IRB Review Process in Multicenter Clinical Trials," http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm080606.pdf .

for them. If a central IRB is responsible for continuing review including evaluation of local issues, the central IRB's procedures should ensure that local issues are addressed. For example, the central IRB may ask the investigator for more information related to subject withdrawals, or decide to visit specific sites to determine the facts in order to assure the safety and welfare of study subjects.

4. Trial Progress

Total Subject Enrollment. The sponsor has primary responsibility for monitoring the study. However, the IRB's responsibility to protect human subjects should include the IRB's review of trial progress. For example, expected rates of enrollment and dropout are generally identified for most studies. A marked difference between the actual and expected rates of enrollment or dropout, either at an individual site or in the study as a whole, may indicate a problem requiring further investigation.

As part of its initial review, the IRB will have approved the protocol, which typically includes the number of subjects expected to be enrolled at a particular site. An investigator who enrolls more subjects than the number allowed at that site may have violated the study protocol or conditions set by the IRB or FDA.

Information about the number of subjects enrolled in the overall study may allow the IRB to ascertain whether enrollment is consistent with the planned number of subjects described in the approved protocol. If enrollment in the study as a whole is too low (either because subject enrollment is too low or subject withdrawal is too high), there may not be justification to continue exposing subjects to the risks of the test article because the study itself may no longer be expected to provide sufficient data to answer the scientific question at hand. (See 21 CFR 56.111(a)(2).)

To address low enrollment issues, an IRB may recommend that the reasons behind the lagging enrollment be explored and appropriate steps be taken to remedy the situation (e.g., proposals for modification of recruitment practices, adjustment of inclusion criteria, evaluation of reasons for excessive withdrawal). In a multi-site study, participating sites might be enrolling subjects at different times. In this case, information about enrollment across all sites may reaffirm that there is sufficient rationale to continue a clinical investigation at an individual site despite low local enrollment. IRBs should note that once the study is completely enrolled, the study should not be unduly prolonged.[16]

Subject Withdrawals. Subjects may withdraw from studies for various reasons (e.g., serious adverse events, conflicts with site staff, transportation problems).

IRB continuing review procedures should provide for review of

- the number of subjects who withdrew from the research at the local site as compared to other sites, and
- a summary of the reasons for the local withdrawals.

[16] See 21 CFR 312.7(c) and 21 CFR 812.7(c).

Information about subject withdrawals may be available in IRB or institutional files, or obtained from other sources (e.g., complaint files, sponsor, clinical investigator, contract research organization (CRO)). IRB review of this information may shed light on problems related to the conduct of the research at the local site.

D. When Expedited Review Procedures May Be Used for Continuing Review

21 CFR 56.110(b) allows for expedited review of research that is included in the list of categories published in the Federal Register[17] and is found to involve no more than minimal risk. This regulation permits continuing review to be conducted using expedited procedures if these requirements are met.

Where a study qualifies for expedited review, review may be conducted by the IRB chairperson or one or more experienced reviewers designated by the chairperson from among the IRB members, who then advise all members of the review decisions made. (See 21 CFR 56.110(b) and (c).)

Disapproval of a study at the time of continuing review can only occur at a convened meeting, not by the expedited review process. The IRB chairperson or his/her designee can approve a study or require modification of the study to secure its approval, but may not disapprove research using the expedited procedures (21 CFR 56.110(b)).

The current list of research eligible for expedited review identifies nine categories of research, the last two of which (8 and 9) apply only to continuing review of research previously approved by the convened IRB (that is, not earlier approved under expedited review). These two categories will be discussed further below. (See Appendix for the list of categories of research eligible for expedited IRB review.)

Under the current list, research that meets the requirements of categories (1) through (7) at the time of review may qualify for expedited review whether that is initial or continuing review. In general, research that qualified for expedited review under one of these seven categories at the time of initial review will continue to qualify for expedited continuing review. However, IRBs should be aware that a 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, a study that previously qualified for expedited review under categories (1)-(7) may require review by the convened IRB if information indicates that the study no longer fits that category or no longer can be said to involve no more than minimal risk. Conversely, research that previously required review (either initial or continuing) by an IRB at a convened meeting may become eligible for expedited review at the time of continuing review, for example if it meets the requirements of categories (8) or (9).

[17] See Appendix for text of 63 FR 60353, November 9, 1998, or at: http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=1998_register&docid=98-29748-filed.pdf .

1. Expedited Review Category (8)

Category (8), which applies only to continuing review, provides that continuing review of research previously approved by the convened IRB (e.g., not originally subject to expedited review) may be eligible for expedited review:

(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.[18]

For a multi-site study, an expedited review procedure may be used by an IRB whenever the conditions of category (8)(a), (b) or (c) are satisfied for the study under continuing review.

For a multi-site study, the various sites will likely have different start dates and rates of enrollment and, thus, may be at different progress points in the trial. As a result, the IRBs for sites that meet the criteria in Expedited Review Category (8) may conduct continuing review using an expedited review procedure, whereas IRBs for sites that do not meet those criteria would need to conduct continuing review of the study at a convened meeting. The IRBs for site(s) performing an ongoing activity such as long-term follow-up or data analysis (e.g., the site operating the coordinating center or statistical center for the study) would need to ensure that continuing review of the study for those sites occurs at least annually. Other sites in a multi-site study may have completed the study and, having no further data analysis or other responsibility in the trial, may be closed out; continuing review for these sites would no longer be necessary.

For a multi-site study in which there is a central IRB, there should be a written agreement delineating the responsibilities of the central IRB and local IRBs.[19] Depending on the terms of any review agreement(s) between the local IRB(s) and the central IRB, it may be possible for the central IRB to provide continuing review for the study for more than one site using expedited review procedures.

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

Under expedited review category (8)(a), FDA interprets "long-term follow-up" to include:

- Research *interactions* that involve no more than minimal risk to subjects (e.g., quality of life surveys); 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.

[18] See 63 FR 60356, November 9, 1998, available at: http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=1998_register&docid=98-29748-filed.pdf.
[19] See "Guidance for Industry - Using a Centralized IRB Review Process in Multicenter Clinical Trials," http://www.fda.gov/RegulatoryInformation/Guidances/ucm127004.htm .

In contrast, FDA 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.

Of note, some 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 study'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)(b)

IRBs conducting continuing review should be aware that if a study previously received expedited continuing review under category (8)(b), but has now begun enrolling subjects, the study may need to be referred for review by the IRB at a convened meeting. The criterion that "no additional risks have been identified" is interpreted by FDA to mean that neither the investigator nor the IRB has identified any additional risks in the research from any relevant source[20] since the IRB's most recent prior review.

Expedited review category (8)(c)

FDA notes that the process for conducting continuing review of research eligible under expedited review category (8)(c) can be accomplished through a simple, abbreviated process. For example, if the study is no longer enrolling subjects, all subjects have completed all protocol required visits, and no new data is being collected, and the investigator's sole activity is data analysis, 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 continuation of the research project for another year without further deliberation or review.

Once the data collection from all trial sites is complete and the overall study results database has been locked and the only remaining activity is analysis of the aggregate data by the study sponsor, further continuing review of the research is generally no longer required.

[20] For example, "any relevant source" would include a review of scientific literature or adverse event reports by the IRB or investigator, as well as communication with FDA or the sponsor.

2. Expedited Review Category (9)

Similar to review category (1)[21] for initial review, 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 (IND) application or an investigational device exemption (IDE);
- Expedited review categories (2) through (8) do not apply to the research;
- The IRB has documented at a convened meeting that the research involves no greater than minimal risk to the subjects; and
- No additional risks 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 present no more than minimal risk to human subjects. With regard to multi-site studies, 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 of the research based on information from any other institution engaged in the research project or from any other relevant source since the IRB's most recent prior review.

E. Frequency of Continuing Review

Under 21 CFR 56.108(a)(2) and 56.109(f), the IRB must determine the frequency of continuing review for each clinical investigation to ensure the continued protection of the rights and welfare of research subjects. FDA regulations at 21 CFR 56.109(f) require an IRB to conduct continuing review of research at intervals appropriate to the degree of risk posed to the subjects, but not less than once a year.

More frequent review (i.e., more frequently than once per year) is appropriate, for example, when the risks to subjects require close monitoring. The IRB should consider the factors set forth below when deciding on an appropriate interval for continuing review. These factors should be outlined in the IRB's written procedures for deciding on the frequency of continuing review:

- The nature of and any risks posed by the clinical investigation;
- The degree of uncertainty regarding the risks involved;

[21] Category 1 research addresses "(1) Clinical studies of drugs and medical devices only when condition (a) or (b) is met: (a) Research on drugs for which an investigational new drug application (21 CFR Part 312) is not required. (Note: Research on marketed drugs that significantly increases the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review.)
(b) Research on medical devices for which (i) an investigational device exemption application (21 CFR part 812) is not required; or (ii) the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling." (63 FR 60353, at 60355, November 9, 1998)

- The vulnerability of the subject population;
- The experience of the clinical investigator in conducting clinical research;
- The IRB's previous experience with that investigator and/or sponsor (e.g., compliance history, previous problems with the investigator obtaining informed consent, prior complaints from subjects about the investigator);
- The projected rate of enrollment; and
- Whether the study involve novel therapies.

At the time of initial approval of the study, FDA recommends that the IRB notify the investigator of the interval at which continuing review will occur (at least annually) and the date by which continuing review must occur. Similarly, at the time of continuing review, the IRB should consider whether the current frequency of continuing review for the study is adequate or should be adjusted. In addition to specifying a time interval, the IRB may also 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. However, if the continuing review interval is described in relation to a subject enrollment number, it must at a minimum also provide for continuing review annually, regardless of the number of subjects enrolled at that time; it is therefore not acceptable to describe the review interval solely in relation to a number of subjects enrolled. The minutes of IRB meetings should clearly document the approval period (continuing review interval).

The IRB's determinations regarding the approval of research must be communicated to the investigator in writing (21 CFR 56.109(e)). This written determination should also notify the investigator of the required interval for, and expected date of, continuing review.

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

Continuing review must occur at intervals appropriate to the degree of risk, but not less frequently than once per year (21 CFR 56.109(f)). IRBs should establish written procedures for informing investigators of the FDA's regulations and the IRB's own policies and procedures on continuing review requirements. (See 21 CFR 56.108(a)(1) & (2).) This applies whether a study is reviewed by the convened IRB or through an expedited process.

The IRB's written procedures should describe how the IRB determines the effective date of approval for the study and how the date and period of approval will be communicated to the clinical investigator.

1. When the IRB Reviews and Initially Approves Research Without Conditions at a Convened Meeting

When the IRB conducts the initial review of a study 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 expiration date of the

initial approval period and the date by which the **first** continuing review must occur may be as late as one year after the date of the IRB meeting at which the research initially was approved (21 CFR 56.109(f)).

2. When the IRB Reviews and Initially 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 that the investigator (a) make specified changes to the research protocol or informed consent document(s), (b) confirm specific assumptions or understandings on the part of the IRB regarding how the research will be conducted, or (c) submit 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 regulations; and
- Directs that the IRB chairperson (or other individual(s) designated by the IRB) 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.

When the IRB reviews and approves research ***with conditions*** at a convened IRB meeting without requiring further review at a subsequent convened meeting, the effective date of the initial approval is the date on which the IRB chairperson (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 investigators. In such circumstances, the expiration date of the initial approval period, which is the date by which the **first** continuing review must occur, may be as late as one year after that effective date of initial IRB approval (see 21 CFR 56.109(f)). (However, an IRB may choose to set the expiration date of the initial approval period at one year from the date of the IRB meeting at which the research project initially was approved with conditions.)

The IRB records must include documentation of the date when the IRB chairperson (or other individual(s) designated by the IRB) determined that all conditions of IRB approval have been satisfied and the approval becomes effective, and the expiration date of the initial IRB approval (i.e., the date by which the first continuing review must occur; see 21 CFR 56.115(a)).

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 (21 CFR 56.109(f)). Given this requirement, it is important to recognize that the use of the "effective date" of IRB approval (i.e., the date on which the IRB chairperson or any other individual(s) designated by the IRB determined that the conditions of

approval have been satisfied) – as opposed to the date of the convened meeting at which the IRB approved a research study with conditions as described above – to determine the latest permissible date for continuing review ***only applies to the first continuing review.***

For all subsequent continuing reviews of research (i.e., the date for the second and all subsequent continuing reviews), if the IRB does *not* follow a procedure for maintaining fixed anniversary dates, the date of the convened meeting when the IRB conducts continuing review and approves the study (with or without conditions) determines the latest permissible date of the next continuing review.

FDA recognizes the logistical advantages of keeping the expiration date of the IRB approval period constant from year to year throughout the life of the research. 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. IRBs 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 procedures.

If the IRB approves research with conditions at the time of continuing review before the expiration date of the preceding IRB approval period, and the investigator works to promptly address and fulfill those conditions, FDA does not intend to object if the investigator needs some additional time, beyond the expiration date of the preceding IRB approval period, to satisfy some or all of the IRB's conditions. FDA would not expect the IRB to report such situations to the Agency.

The same guidelines for determining the continuing review dates would apply when the IRB determines that research must undergo continuing review more often than annually and when the IRB reviews and approves research under an expedited review procedure, in accordance with 21 CFR 56.110.

At the time of continuing review, the IRB must consider whether the current frequency of continuing review for the study is appropriate to the degree of risk or should be adjusted (21 CFR 56.109(f)). 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 21 CFR 56.111 remain satisfied, but require that the next continuing review occur in 6 months.

FDA recommends that the IRB's written procedures provide for sufficient advance notice to the investigator to ensure that the requirements for continuing review, by the anniversary or other date identified for the next continuing review, are met. The IRB should also develop administrative procedures to ensure that continuing review meetings are not only scheduled but occur before the necessary date and may use a tracking system to minimize any unintended expiration of IRB approval. FDA cautions, however, that if investigators submit materials for continuing review too far in advance of the expiration date of the IRB approval, the materials

may not reflect the current status of the study by the time that continuing review actually takes place. The IRB therefore should work to link as closely in time as possible: 1) the receipt by the IRB of continuing review materials; 2) the review of those materials by the IRB; and 3) the impending expiration date for IRB approval. Nevertheless, it is the investigator's responsibility to ensure that the study complies with applicable regulations.[22] Therefore, to ensure that IRB approval is maintained (without which the study cannot continue), the investigator should provide the information the IRB needs to perform its continuing review function in a timely and complete manner, whether or not the IRB provides any reminders.

Review of an amendment to a protocol during the period for which approval is authorized does not constitute continuing review of the study as a whole, and thus does not extend the date by which continuing review must occur (i.e., not more than one year from the original approval date or most recent continuing review approval date).

G. Communicating the IRB's Continuing Review Determination

Under 21 CFR 56.109(e), the IRB must "notify investigators and the institution in writing of its decision to approve or disapprove the proposed research activity, or of modifications required to secure IRB approval of the research activity. If the IRB decides to disapprove a research activity, it shall 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."

After an IRB completes its continuing review, the IRB must provide written notification informing the investigator of the IRB's determination (e.g., approval, approval with modification(s) to secure approval, disapproval; 21 CFR 56.109(e)). For studies that are approved to continue, FDA recommends that the notification clearly state the date when approval is effective, the period of time for which the study is approved, and the next continuing review date.

When approving research with conditions at the time of continuing review, the IRB's notification should state 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. (Note that FDA would not consider such a suspension of subject enrollment at the time of continuing review to be a suspension of IRB approval that needs to be reported to appropriate institutional officials, the head (or designee) of the agency conducting or supporting the research, or FDA under 21 CFR 56.113.)

FDA recommends that IRBs notify the sponsor of any decision to disapprove the research and the reason(s) for the disapproval determination although they are not generally required to do

[22] See 21 CFR 312.53(c)(1)(vii); 312.60; 312.66; 812.36(c)(viii), 812.100, 812.110(b), 812.40, and 812.43(c)(4)(i).

so.[23] FDA encourages sponsors, clinical investigators, and IRBs to communicate with one another to protect the rights and welfare of study subjects.

H. Lapse, Suspension, or Termination of IRB Approval of Research

1. Lapse of IRB Approval

As discussed previously, the agency 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 period specified by the IRB. FDA 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.

FDA regulations at 21 CFR part 56 make no provision for any grace period extending the conduct of research beyond the expiration date of IRB approval. When continuing review of the research does not occur prior to the end of the approval period specified by the IRB, IRB approval expires automatically. A lapse in IRB approval of research occurs whenever an investigator has failed to provide continuing review information to the IRB or the IRB has not conducted continuing review and re-approved the research by the expiration date of IRB approval. In such circumstances, all research activities involving human subjects must stop. Enrollment of new subjects cannot occur after the expiration of IRB approval.[24]

FDA expects that IRB procedures will be followed by investigators such that lapses of IRB approval will be a rare occurrence. However, temporarily continuing participation of already enrolled subjects in a research project during the period when IRB approval has lapsed may be necessary or appropriate, for example, when the research interventions hold out the prospect of direct benefit to the subjects (e.g., investigational chemotherapy regimen in an oncology trial), or when withholding those interventions poses increased risk to the subjects.[25] If the IRB decides that already enrolled subjects should continue to receive the interventions that were being administered to subjects under the research protocol, data collection (especially safety information) should also continue for such subjects (e.g., implantable device requiring long-term follow-up).

If the investigator is initially determining whether it is in the best interests of already enrolled subjects to continue to participate in the research after IRB approval has expired, the investigator should consult the treating physician (if the investigator is not the treating physician). This determination may be made for all enrolled subjects as a group or for individual subjects. In all

[23]For studies involving an exception from informed consent for emergency research conducted under 21 CFR 50.24, an IRB must notify both the clinical investigator and the sponsor in writing of the IRB's determination that it cannot approve a study (21 CFR 50.24(e) and 56.109(e)).

[24] See, for example, 21 CFR 56.103(a) (studies that must meet requirements for prior submission in parts 312, 812, and 813 "shall not be initiated unless that investigation has been reviewed and approved by, and remains subject to continuing review by, an IRB meeting the requirements of this part"); 21 CFR 812.110 (a) (investigator shall not request the written informed consent of any subject to participate, and shall not allow any subject to participate before obtaining IRB and FDA approval); 21 CFR 312.66 (requiring investigators to assure that study is subject to continuing review by an IRB meeting the requirements of part 56).

[25] See 21 CFR 56.102(g).

cases, the investigator should verify that the IRB agrees with this determination as soon as possible.

We recommend that IRB procedures address how the investigator's determinations will be reviewed. FDA recommends that the procedures cover whether the IRB's review may be made by the IRB chairperson, by another IRB member or group of IRB members designated by the IRB chairperson, or at a convened meeting of the IRB. In addition, the procedures should address whether the investigator's determination applies to one or more individuals or all enrolled subjects, timeframes, etc.

When IRB approval of ongoing research lapses and the investigator wants to continue the study, the IRB should complete continuing review for the study as soon as possible. Investigators may resume the study once continuing review and approval by the IRB has occurred. The IRB should document why the lapse occurred (e.g., insufficient number of IRB meetings to accommodate all continuing reviews, investigator failure to respond to a reminder notice of the anniversary date of approval, investigator failure to provide information to allow the IRB to conduct continuing review) and identify the steps taken to prevent any future lapses (e.g., modification of written procedures, adding more IRB meetings).

When IRB approval of an ongoing study lapses and the IRB subsequently re-approves the research, the IRB may approve the study for one year and establish a new anniversary date for the expiration date of subsequent approval periods. The IRB may also re-approve the research for a period of less than 1 year, either to retain the original anniversary date on which prior approval periods expired or to address study risks, in which case, a new date for continuing review is likely.

The lapse of IRB approval due to a failure to complete continuing review and obtain reapproval prior to expiration of the prior approval does not automatically constitute a suspension or termination of IRB approval, for reporting purposes under 21 CFR 56.113.[26] However, the failure to meet continuing review obligations may be grounds for suspension or termination under 21 CFR 56.113 (described below), in particular where the lapse of approval is not the first to occur in a study. If the IRB notes a pattern of non-compliance with the requirements for continuing review (e.g., an investigator repeatedly or deliberately neglects to submit materials for continuing review in a timely fashion or the IRB itself is not meeting the continuing review dates), the IRB should determine the reasons for the non-compliance and take appropriate corrective actions. The IRB must report to FDA any instance of serious or continuing non-compliance with FDA regulations or IRB requirements or determinations, and any suspension or

[26] Conducting a study subject to IRB oversight during a period of lapsed approval, however, is a violation of an investigator's duties under FDA regulations. See 21 CFR 312.60 (investigator is responsible for ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations); 312.66 (requiring investigators to assure that study is subject to continuing review by an IRB meeting the requirements of part 56); 21 CFR 812.100 (investigators must ensure that study is conducted in accordance with applicable FDA regulations and conditions of IRB approval); 812.110(a) (investigator shall not request the written informed consent of any subject to participate, and shall not allow any subject to participate before obtaining IRB and FDA approval); 21 CFR 56.103(a) (studies that must meet requirements for prior submission in parts 312, 812, and 813 "shall not be initiated unless that investigation has been reviewed and approved by, and remains subject to continuing review by, an IRB meeting the requirements of this part").

termination of IRB approval (21 CFR 56.108(b)(2) and (3), and 56.113). FDA will evaluate such reports and may inspect the site, investigator, or IRB, as appropriate, to assess compliance with FDA's human subject protection regulations.

FDA also recommends that the IRB notify the sponsor of any instance of serious or continuing non-compliance with FDA regulations or IRB requirements or determinations, and any suspension or termination of IRB approval. Among the general responsibilities of sponsors is the assurance of proper monitoring of the investigation (21 CFR 312.50 and 21 CFR 812.40) and the selection of qualified investigators (21 CFR 312.53(a) and 21 CFR 812.43(a)). Informing sponsors of investigator non-compliance or IRB suspension or termination of the study allows the sponsor the opportunity to address these concerns. For example, the sponsor could work with the investigator to transfer subjects to another site in the local area, find a replacement investigator at the current site, or ensure that the study is terminated in an orderly manner.

2. Suspension or Termination of IRB Approval

The IRB has the authority to suspend or terminate approval of clinical investigations:

- that are not conducted in accordance with the IRB's requirements (21 CFR 56.113); or
- that are associated with unexpected serious harm to subjects (21 CFR 56.113).

Suspension of 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 investigator misconduct or a safety issue that needs further investigation and evaluation, the IRB may decide to suspend the study until the matter is resolved. In addition, the IRB may determine whether it is appropriate to notify subjects, and if so, when, given that complete information may not be available when the IRB first becomes aware of the issue.

For multi-site studies in which a local IRB is responsible for review of research at a given site, the local IRB's decision to suspend or terminate its approval of the research only applies to the conduct of the research project at the site under its review. On the other hand, if many or all sites engaged in a multi-site study rely upon a central IRB for review of the research, the central IRB could suspend or terminate its approval of the research either at one site because of a problem regarding the conduct of the research at that site, or at all sites under its review because of a study-wide problem. If an IRB (whose authority is only over a single site) believes the problem it found may be present at other sites, the IRB should inform FDA of its concern in the suspension or termination notification.

Any suspension or termination of IRB approval must include the reasons for the IRB's actions and be promptly reported to the clinical investigator, institutional officials, and the FDA (21 CFR 56.113). IRBs must follow written procedures for ensuring such reporting (21 CFR 56.108(b)(3)).

When reporting suspensions or terminations of IRB approval to FDA, IRBs should include:

- the name of the drug, biologic, or device;

- the IND number; or the IDE number/non-significant risk (NSR) status of the device;
- the full name of the research protocol;
- the name(s) and address(es) of the clinical investigator(s);
- the reason(s) for the suspension or termination; and
- information about the IRB's investigation and action plan to prevent/address future non-compliance.

IRBs that have concerns about suspension or termination of approval of studies may contact FDA at any time to discuss these issues.[27]

When a study is suspended or terminated by the IRB, the IRB should consider the need to inform current or previously enrolled study subjects, as appropriate, about the action. In addition, an IRB should have established 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, should the IRB (a) suspend or terminate its approval during the period for which IRB approval had already been given, or (b) disapprove a study at the time of continuing review. For example, the IRB, in consultation with the investigator and the subjects' treating physicians (if different from the investigator), may need to determine whether it is in the best interests of currently enrolled subjects to (a) continue receiving the interventions that were being administered to subjects under the study at the present site, (b) be transferred to another study-site so that participation of the subjects in the study may continue, or (c) be transitioned to medical management outside of the research context. Continuation of subjects on the test article may be appropriate, for example, when the test article holds out the prospect of direct benefit to the study subjects or when withholding the test article poses increased risk to study subjects. If the IRB decides that enrolled subjects should continue to receive the test article, it should also ensure that data collection (especially safety information) continues for such subjects. If follow-up of currently enrolled subjects is necessary to ensure their rights, safety or welfare, the IRB should ensure that the investigators inform the subjects, and report any unanticipated problems to the IRB, the sponsor, and the FDA (see 21 CFR 56.108(b)).

[27] See http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm134493.htm for FDA points of contact to which IRB suspensions or terminations may be reported.

Appendix

CATEGORIES OF RESEARCH THAT MAY BE REVIEWED BY THE INSTITUTIONAL REVIEW BOARD (IRB) THROUGH AN EXPEDITED REVIEW PROCEDURE[\1\]

[Federal Register: November 9, 1998 (Volume 63, Number 216)] [Notices] [Page 60353-60356][*]

The list that is referenced in Sec. 56.110(a) was originally published in the Federal Register of January 27, 1981 (46 FR 8980), as a notice of a list of research activities that could be reviewed by the IRB through the expedited review procedures set forth in the FDA's regulations. OPRR has a separate codification that references the Expedited Review List for matters under the Department of Health and Human Services' (HHS) jurisdiction (45 CFR part 46). The HHS list was published in the Federal Register on January 26, 1981 (46 FR 8392). The FDA and HHS lists published in 1981 differ slightly, in that item nine on the HHS list, concerning research on individual or group behavior, pertains only to 45 CFR 46.110. Because behavioral research is not specifically regulated by FDA, that category was not included in the list published by FDA.

Applicability

(A) Research activities that (1) present no more than minimal risk to human subjects, and (2) involve only procedures listed in one or more of the following categories, may be reviewed by the IRB through the expedited review procedure authorized by 45 CFR 46.110 and 21 CFR 56.110. The activities listed should not be deemed to be of minimal risk simply because they are included on this list. Inclusion on this list merely means that the activity is eligible for review through the expedited review procedure when the specific circumstances of the proposed research involve no more than minimal risk to human subjects. (B) The categories in this list apply regardless of the age of subjects, except as noted. (C) The expedited review procedure may not be used where identification of the subjects and/or their responses would reasonably place them at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, insurability, reputation, or be stigmatizing, unless reasonable and appropriate protections will be implemented so that risks related to invasion of privacy and breach of confidentiality are no greater than minimal. (D) The expedited review procedure may not be used for classified research involving human subjects. (E) IRBs are reminded that the standard requirements for informed consent (or its waiver, alteration, or exception) apply regardless of the type of review--expedited or convened--utilized by the IRB. (F) Categories one (1) through seven (7) pertain to both initial and continuing IRB review.

[\1\] An expedited review procedure consists of a review of research involving human subjects by the IRB chairperson or by one or more experienced reviewers designated by the chairperson from among members of the IRB in accordance with the requirements set forth in 45 CFR 46.110.

[*] The list may be viewed online via GPO Access at http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=1998_register&docid=98-29748-filed.pdf

Research Categories

(1) Clinical studies of drugs and medical devices only when condition (a) or (b) is met. (a) Research on drugs for which an investigational new drug application (21 CFR Part 312) is not required;

(Note: Research on marketed drugs that significantly increases the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review.)

(b) Research on medical devices for which (i) an investigational device exemption application (21 CFR Part 812) is not required; or (ii) the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.

(2) Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows: (a) From healthy, nonpregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 ml in an 8 week period and collection may not occur more frequently than 2 times per week; or (b) from other adults and children,[\2\] considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period and collection may not occur more frequently than 2 times per week.

(3) Prospective collection of biological specimens for research purposes by noninvasive means. Examples: (a) hair and nail clippings in a nondisfiguring manner; (b) deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction; (c) permanent teeth if routine patient care indicates a need for extraction; (d) excreta and external secretions (including sweat); (e) uncannulated saliva collected either in an unstimulated fashion or stimulated by chewing gumbase or wax or by applying a dilute citric solution to the tongue; (f) placenta removed at delivery; (g) amniotic fluid obtained at the time of rupture of the membrane prior to or during labor; (h) supra- and subgingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylatic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques; (i) mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings; (j) sputum collected after saline mist nebulization.

(4) Collection of data through noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. Where medical devices are employed, they must be cleared/approved for marketing. (Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared medical devices for new indications.) Examples: (a) physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the subject or an invasion of the subject's privacy; (b) weighing or testing sensory acuity; (c) magnetic resonance

[\2\] Children are defined in the HHS regulations as ``persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted." 45 CFR 46.402(a).

imaging; (d) electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, doppler blood flow, and echocardiography; (e) moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.

(5) Research involving materials (data, documents, records, or specimens) that have been collected or will be collected solely for nonresearch purposes (such as medical treatment or diagnosis).

(Note: Some research in this category may be exempt from the HHS regulations for the protection of human subjects. 45 CFR 46.101(b)(4). This listing refers only to research that is not exempt.)

(6) Collection of data from voice, video, digital, or image recordings made for research purposes.

(7) Research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies.

(Note: Some research in this category may be exempt from the HHS regulations for the protection of human subjects. 45 CFR 46.101(b)(2) and (b)(3). This listing refers only to research that is not exempt.)

(8) Continuing review of research previously approved by the convened IRB as follows: (a) Where (i) the research is permanently closed to the enrollment of new subjects; (ii) all subjects have completed all research-related interventions; and (iii) the research remains active only for long-term follow-up of subjects; or (b) Where no subjects have been enrolled and no additional risks have been identified; or (c) Where the remaining research activities are limited to data analysis.

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