Guidance for IRBs, Clinical Investigators, and Sponsors

IRB Continuing Review after Clinical Investigation Approval

DRAFT GUIDANCE

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For questions regarding this draft document contact Sara Goldkind, MD, Office of Good Clinical Practice, HF-34, 301-827-3340.

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Procedural

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

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Contains Nonbinding Recommendations

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

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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This draft guidance is intended to assist institutional review boards (IRBs) in carrying out their continuing review responsibility under 21 CFR 56.108(a) and 56.109(f) by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 subjects in clinical investigations. The draft guidance should also help clinical investigators and sponsors better understand their responsibilities related to continuing review. When finalized, this document will supersede the Information Sheet, *Continuing Review After Study Approval* (September 1998, Office of Health Affairs, Food and Drug Administration).

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).

II. BACKGROUND

FDA's IRB regulations were first issued in 1981, when the single investigator-single site study 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 a study. Since that time, multi-site studies have become commonplace. Although an individual investigator informs the IRB about events at his 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.

III. DISCUSSION

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 and 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 these written procedures is to ensure that IRBs have a framework for periodically reviewing the conduct of investigations by clinical investigators. While an investigation is ongoing, IRBs review and consider changes to research as they are received, including protocol amendments.[2] They also review informed consent form changes,[3] reports of unanticipated problems,[4] and other information about the investigation. 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] See 21 CFR 56.108(a)(3) and (4); 56.109(a); 56.110(b)(2).
[3] See 21 CFR 56.109(b).
[4] See 21 CFR 56.108(b)(1).

(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)). (See Section D. of this guidance for more information on application of expedited review procedures to continuing review.)

IRBs involved in multi-site studies may use cooperative review agreements or other mechanisms (e.g., using a centralized IRB review process (CIRB)) to reduce or eliminate duplication of effort and to improve consistency of the continuing review process (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.[5] Other agreements may assign responsibility for local issues to the institution's IRB, but assign the remaining aspects of continuing review to a CIRB. Whatever the arrangement, the IRB(s) responsible for continuing review should obtain and review information across the entire study.

For purposes of continuing review of multi-site studies, FDA recommends that reviewing IRBs obtain information from the study sponsor. Sponsors are in the unique position of having information for the entire study that may assist IRBs in reviewing the studies and protecting subjects. The IRB may ask the sponsor of drug and biologics studies to provide the IRB with reports for the entire study to fulfill recommendations included in this guidance document. Sponsors of investigational drug studies are required by 21 CFR 312.33 to submit annual reports to FDA on the progress of their studies and should therefore be able to provide copies of those reports to the reviewing IRBs. 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)).

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;

[5] 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). .

- 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 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 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, etc.) (See 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).) 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. (See 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 thus should provide confirmation that conflicted members did not inappropriately participate in the IRB's continuing review of their studies (21 CFR 56.115((a)(2)).

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 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.

We recommend that the IRB's written procedures call for submission of the following information for consideration by the IRB in continuing review:

- the version of the protocol and informed consent document(s) in use at the site;
- any proposed modifications to the protocol and/or informed consent document;
- a written summary, if available, of amendments to the research since the last review;
- the Investigator's Brochure, if available, including any modifications;
- any new and relevant information, published or unpublished, especially information about risks associated with the research; for example, a summary of any unanticipated problems[6] and available information regarding adverse events; (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).)
- aggregate information about relevant regulatory actions occurring during the past year 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));
- any other significant information, such as reports from data monitoring committees (DMCs)[7], if available;
- a summary of any subject withdrawals from the research since the last IRB review;
- a summary of any complaints about the research from subjects enrolled at the local site since the last IRB review.

Note that much of the above information is often included in annual reports prepared by study sponsors.[8] If the information is included in the annual report, the information may be provided by supplying the IRB with a copy of that report; a separate document need not be prepared.

An IRB that is conducting continuing review should be knowledgeable of the materials related to the investigation, including those associated with previous reviews (ad hoc as well as scheduled reviews) or 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.

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[6] 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)).

[7] FDA's guidance on DMCs can be accessed at http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126578.pdf

[8] 21 CFR 312.33 and 812.150(b)(5)

For a multi-site study, FDA recommends that sponsors provide IRBs directly with information from the entire study, data monitoring committee (DMC) reports, and any other information about the test article that would be pertinent to the IRB's continuing review. 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.[9]

An IRB other than the IRB that conducted the initial review may perform continuing review of a study. However, an IRB that conducted the initial review may be best suited to conduct continuing review because of its familiarity with the study and/or previous review(s).

An IRB's written procedures may include measures that reduce burdens and allow the IRB to efficiently accomplish its continuing review workload. At the same time, the IRB's procedures should allow studies undergoing continuing review to be considered and discussed individually, and should not deprive members of the ability to vote "yes" on some studies and "no" on others. 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.
- 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").

C. Key Topics to Consider During Continuing Review

When conducting continuing review, the IRB should start with the working assumption that the research, as previously approved, does satisfy all of the criteria under §56.111. The IRB should focus on any new information provided by the investigator or sponsor, or otherwise available to the IRB, that would alter the IRB's prior determinations, particularly with respect to: 1) Risk Assessment; 2) Adequacy of the Process for Obtaining Informed Consent; 3) Local Issues, and 4) Trial Progress.

[9] 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.)

1. Risk Assessment

As previously discussed, during continuing review, the IRB must determine that the criteria necessary for IRB approval continue to be met under 21 CFR 56.111. 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 information from either the clinical investigator or the sponsor that has been received since the date that the IRB last reviewed the study, including the sponsor's annual report, any analysis by the sponsor performed since then, new information, etc. (See Section III.B.) During continuing review, IRBs should review this information and determine whether the risks to subjects are still minimized and whether the risks of the study are still reasonable in relation to the anticipated benefits.

2. Adequacy of Process for Obtaining 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 that an IRB use 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 ensure that the currently approved consent document or any revised consent document proposed for approval meets the criteria in 21 CFR 50.25, including the requirement to include any reasonably foreseeable risks.[10] The IRB's continuing review may reveal new risk information that will require updating of informed consent materials in order to satisfy these requirements. In addition, the IRB should ensure that, if significant new findings have developed during the course of the research which may relate to the subjects' willingness to continue participation, this information will be provided to enrolled subjects (e.g., important toxicity information, adverse event information identified during analysis of reports across all sites.)

In a multi-site trial, a CIRB may be reviewing the adequacy of informed consent, depending on the agreement between the local IRB and the CIRB. The CIRB may accomplish this function by reviewing the model/template informed consent document during the course of the study or for continuing review of site-specific informed consent documents in use at one or more, or even all, individual sites.[11]

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[10] See 21 CFR 56.111(a)(4-5).

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

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, standards of professional conduct or practice;
- Reports from third party observation of the research, carried out under 21 CFR 56.109(f).

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 for them. If a CIRB is responsible for continuing review including evaluation of local issues, the CIRB's procedures should ensure that local issues are addressed. For example, the CIRB may ask the investigator for more information related to subject withdrawals, or decide to visit specific sites to determine the facts and 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 trial as a whole may indicate a problem with the study requiring further investigation.

As part of its initial review, the IRB will have approved the protocol, which generally 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 a condition of IRB and FDA approval.

Information about the number of subjects enrolled in the overall trial 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), it may not be possible for the study to meet its stated objectives, and therefore the study may no longer be ethical because risks to subjects may exceed the anticipated benefits, if any, to subjects, and the importance of the

knowledge that may be expected to result (See §56.111(a)(2)). That is, 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. To address low enrollment issues, an IRB may recommend that the reasons behind the lagging enrollment be explored by the sponsor 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, etc.). Alternatively, for a multi-site trial, 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.

Once the enrollment goals for the study have been reached, the study should be reassessed to determine if data are indeed sufficient to answer the scientific question raised by the study. A sponsor is prohibited from unduly prolonging a study if the results of the investigation appear to establish sufficient data to support a marketing application. (See 21 CFR 312.7(c) and 812.7(c).)

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.

Information about subject withdrawals may be available in IRB or institutional files, or obtained from other sources (e.g., 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[12] 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.

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.

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

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 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, 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).

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.

(63 FR 60356, November 9, 1998).

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.

For trials that meet the provisions of category (8)(a) or (c) and are subject to a review agreement with a CIRB, consideration may be given to closing out the study at all sites except for the CIRB, provided that does not breach the terms of any review agreement(s). That is, the CIRB could provide continuing review for the study using expedited review procedures when the research activity is limited to long-term follow-up of subjects (category 8(a)) or analysis of the data (category 8(c)). Similarly, for multi-site trials that do not involve use of a CIRB, when the remaining research activity is limited to long-term follow-up or data analysis, only the site(s) engaged in the long-term follow-up or ongoing data analysis would need to have continuing IRB review, and it could be handled via expedited review.

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

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 or require modification in (to secure approval of) a study, but may not disapprove research using the expedited procedures (21 CFR 56.110(b)).

Expedited Review Category (9)

Similar to review category (1) 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 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 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 following factors 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 risks posed by the clinical investigation;
- The degree of uncertainty regarding the risks involved;
- The vulnerability of the subject population;
- The experience of the clinical investigator in conducting clinical research;
- The IRB's previous history with that investigator and/or sponsor;
- The projected rate of enrollment; and
- Whether the studies involve novel therapies.

At the time of initial approval of the clinical investigation, the IRB should specify the appropriate interval at which continuing review will occur (at least annually), and communicate this to the investigator. 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).

F. Determining Continuing Review Dates

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)). We recommend that the IRB establish written procedures for informing investigators of the FDA's regulations and the IRB's own policies and procedures on continuing review requirements. This applies whether the studies are 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 protocol (e.g., the date of the IRB meeting that reviewed the original study, the

date of the approval letter) and how the date and period of approval will be communicated to the clinical investigator.

FDA recommends that the IRB's written procedures provide for sufficient advance notice to the clinical investigator to ensure that the requirements for continuing review, by the anniversary date, are met. The IRB should develop administrative procedures 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.

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).

FDA notes that it may be less confusing to researchers if the same anniversary date for continuing review can be preserved, year to year. At the time of continuing review, however, the IRB should consider whether the current frequency of continuing review for a study is appropriate or should be adjusted. If the IRB determines that risks posed to study subjects have increased and the study requires continuing review more frequently than it is being conducted, the IRB can change the period of approval for the study, and the next continuing review date.

Note that for studies that are also subject to regulation under 45 CFR part 46, such as studies that are funded or conducted by the Department of Health and Human Services (HHS), the HHS Office for Human Research Protections (OHRP) has issued guidance on continuing review which includes information intended to assist IRBs in determining dates by which continuing review should occur in order to comply with regulations at 45 CFR 46.109(e), which also require that such review occur not less frequently than once per year.
(See http://www.hhs.gov/ohrp/).

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, withdrawal of approval). For studies that are approved to continue, FDA recommends that the notification clearly state the date when approval is effective (with attention to requirements to meet any conditions placed on the research by the IRB), the period of time for which the study is approved, and the next continuing review date.

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

Lapse 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. If an IRB determines that the approval for a site has lapsed, the IRB should conduct continuing review for the site according to its established written procedures as soon as possible. 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). 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.

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.[13] 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-

[13] However, conducting a study subject to IRB oversight during a period of lapsed approval is a violation of an investigator's duties under FDA regulations. See 21 CFR 312.66 (requiring investigator to assure that study is subject to continuing review by an IRB meeting the requirements of part 56) 812.100 (investigators must ensure that study is conducted in accordance with applicable FDA regulations and conditions of IRB approval); 56.103(b) (studies that must meet requirements for prior submission in part 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.")

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

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.

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); and
- the reason(s) for the suspension or termination.

IRBs that have concerns about suspension or termination of approval of studies may contact FDA at any time to discuss these issues.[14]

When IRB approval of a clinical investigation is suspended or terminated, IRBs 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 during any period in which the IRB and clinical investigator are attempting to resolve any remaining issues. For example, the IRB should determine on a case by case basis whether currently enrolled subjects should

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

continue receiving the test article, be transferred to another investigator or site, or obtain care from a health care provider who is not part of the clinical investigation. 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)).