



[Home](#) > [Regulatory Information](#) > [Guidances](#)

Regulatory Information

Continuing Review After Study Approval - Information Sheet

Information Sheet - Guidance for Institutional Review Boards and Clinical Investigators (Continuing Review After Study Approval)

Institutional Review Boards (IRBs) are responsible for continuing review of ongoing research to ensure that the rights and welfare of human subjects are protected. The Food and Drug Administration (FDA) regulations regarding continuing review 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 per year [21 CFR 56.108(a)(1) and 56.109(f)];
- determining which studies need verification from sources other than the investigator that no material changes in the research have occurred since the previous IRB review [21 CFR 56.108(a)(2)];
- ensuring that changes in approved research are promptly reported to, and approved by, the IRB [21 CFR 56.108(a)(3-4)]; and
- suspending or terminating approval of research that is not being conducted in accordance with the IRB's requirements [21 CFR 56.108(b)(2) and 56.113].

The FDA continuing review regulations outline minimum requirements; they do not provide specific instructions to IRBs on how to set up their own rules for continuing review within the framework of the regulations. Therefore, the regulations allow institutions or IRBs to impose greater and more detailed standards of protection for human subjects than those specified by the regulations and permit each IRB to develop procedures appropriate to its needs. By regulation, the IRB has the authority and the responsibility to take appropriate steps such as terminating or suspending approval of research that is not being conducted in accordance with the IRB's requirements.

1. Criteria for Conducting Continuing Review

FDA regulations set forth the criteria to be satisfied if an IRB is to approve research [21 CFR 56.111]. These criteria are the same for initial review and continuing review and include a determination by the IRB that

- risks to subjects are minimized;
- risks to subjects are reasonable in relation to anticipated benefits;
- selection of subjects is equitable;
- informed consent is adequate and appropriately documented;
- where appropriate, the research plan makes adequate provision 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; and
- appropriate safeguards have been included to protect vulnerable subjects.

2. Process for Conducting Continuing Review

Routine continuing review should include IRB review of a written progress report(s) from the clinical investigator. Progress reports include information such as: the number of subjects entered into the research study; a summary description of subject experiences (benefits, adverse reactions); numbers of withdrawals from the research; reasons for withdrawals; the research results obtained thus far; a current risk-benefit assessment based on study results; and any new information since the IRB's last review. Special attention should be paid to determining whether new information or unanticipated risks were discovered since the previous IRB review. Any significant new findings which may relate to the subjects' willingness to continue participation should be provided to the subjects in accordance with 21 CFR 50.25(b)(5).

The IRB should obtain a copy of the consent document currently in use and determine whether the information contained in it is still accurate and complete, including whether new information that may have been obtained during the course of the study needs to be added. Obtaining the consent document also provides a check on whether the document being used by the clinical investigator has current IRB approval.

The purpose of continuing review is to review the progress of the entire study, not just changes in it. Continuing review of a study may not be conducted through an expedited review procedure, unless 1) the study was eligible for, and initially reviewed by, an expedited review procedure, or 2) the study has changed such that the only activities remaining are eligible for expedited review.

The IRB should determine that the frequency and extent of continuing review for each study is adequate to ensure the continued protection of the rights and welfare of research subjects. The factors considered in setting the frequency of review

may include: the nature of the study; the degree of risk involved; and the vulnerability of the study subject population. Note that 21 CFR 56.108(a)(2) requires IRBs to follow written procedures for determining the frequency and extent of continuing review.

The continuation of research after expiration of IRB approval is a violation of the regulations [21 CFR 56.103(a)]. If the IRB has not reviewed and approved a research study by the study's current expiration date, i.e., IRB approval has expired, research activities should stop. No new subjects may be enrolled in the study. However, if the investigator is actively pursuing renewal with the IRB and the IRB believes that an over-riding safety concern or ethical issue is involved, the IRB may permit the study to continue for the brief time required to complete the review process.

When study approval is terminated by the IRB, in addition to stopping all research activities, any subjects currently participating should be notified that the study has been terminated. Procedures for withdrawal of enrolled subjects should consider the rights and welfare of subjects. If follow-up of subjects for safety reasons is permitted/required by the IRB, the subjects should be so informed and any adverse events/outcomes should be reported to the IRB and the sponsor.

3. Process for Dealing with Reports of Adverse Reactions and Unexpected Events

a. Written Procedures

IRB continuing review responsibilities include reviewing reports of adverse reactions and unexpected events involving risks to subjects or others. The IRB should establish a procedure for receiving and reviewing these reports. The level and promptness of review may depend upon factors such as the seriousness of the event, whether the event is described in the study protocol and consent and whether the event occurred at a location for which the IRB is the IRB of record. The written procedures may include a brief form to be completed by the principal investigator when an adverse event occurs, asking for his/her opinion as to whether the event was related to the study and other information to aid the IRB in an appropriate and efficient review of the event.

Researchers should be made aware of the IRB's policies and procedures concerning reporting and continuing review requirements. This can be accomplished by notifying the investigator, in the IRB's letter of approval, of the requirement to report changes and unanticipated problems in research activities. The IRB's written procedures pertaining to continuing review and reporting requirements should be distributed to ensure that all individuals involved in research activities understand their obligations.

b. Process

Unanticipated risks are sometimes discovered during the course of research. Information that may impact on the risk/benefit ratio should be promptly reported to, and reviewed by, the IRB to ensure adequate protection of the welfare of the subjects. Based upon such information, the IRB may need to reconsider its approval of the study, require modifications to the study or, revise the continuing review timetable.

IRBs are also responsible for ensuring that reports of unanticipated problems involving risks to human subjects or others are reported to the FDA [21 CFR 56.108(b)(1)]. Usually, this reporting is accomplished through the normal reporting channel, i.e., the investigator to the sponsor to FDA.

4. Process for Reviewing Changes in Ongoing Research During the Approval Period

In accord with 21 CFR 56.110(b), an IRB may use expedited review procedures to review minor changes in ongoing previously-approved research during the period for which approval is authorized. An expedited review may be carried out by the IRB chairperson or by one or more experienced reviewers designated by the chairperson from among members of the IRB.

When a proposed change in a research study is not minor (e.g., procedures involving increased risk or discomfort are to be added), then the IRB must review and approve the proposed change at a convened meeting before the change can be implemented. The only exception is a change necessary to eliminate apparent immediate hazards to the research subjects [21 CFR 56.108(a)(4)]. In such a case, the IRB should be promptly informed of the change following its implementation and should review the change to determine that it is consistent with ensuring the subjects' continued welfare.

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