

**OFFICE OF RESEARCH AND DEVELOPMENT
VETERANS HEALTH ADMINISTRATION**

GUIDANCE ON CONTINUING REVIEW FOR INSTITUTIONAL REVIEW BOARDS

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SCOPE: This guidance applies to all VA research involving human subjects under Institutional Review Board (IRB) oversight as described in VHA Handbook 1200.05. VHA Handbook 1200.05 operationalizes Common Rule (38 CFR Part 16) requirements for continuing review in VA research. Continuing review is intended as a means to evaluate the conduct of a study and to verify that risks are minimized and still reasonable in relation to the potential benefits. The IRB is required to review all projects at least once per year but may want to review others at more frequent intervals. Throughout the life of the project, the principal investigator (PI) also has a duty to report any changes in the project as well as any unanticipated problems per the IRB's requirements.

1. How does the IRB determine the frequency for continuing review?
2. What materials must the PI submit to the IRB?
3. What does the IRB review?
4. When can the IRB use expedited procedures for continuing review?
5. What happens if there is a lapse of approval?

1. HOW DOES THE IRB DETERMINE THE FREQUENCY FOR CONTINUING REVIEW?

VHA Handbook 1200.05 requires that the IRB must establish written standard operating procedures (SOPs) that include, but are not limited to, procedures for conducting initial and continuing review of research and reporting findings and actions to the investigator and to the Research and Development (R&D) Committee. The Common Rule (38 CFR Part 16) also requires that the IRB conduct continuing review at intervals appropriate to the degree of risk but not less than once per year. The IRB should decide the frequency of continuing review for each research project necessary to ensure the continued protection of the rights and welfare of research subjects. More frequent review (i.e., more frequently than once per year) may be appropriate when the risks to subjects warrant more frequent reassessment. The IRB should consider factors such as the following when deciding on an appropriate interval for continuing review and these factors should be outlined in the IRB's standard operating procedures:

- The nature of any risks posed by the research project;
- The degree of uncertainty regarding the risks involved;
- The vulnerability of the subject population;
- The experience of the investigators in conducting this type of research;
- The IRB's previous experience with the investigators (e.g., compliance history, previous problems with the investigator obtaining informed consent, or prior complaints from subjects about the investigator);
- The projected rate of enrollment; and
- Whether the research project involves novel interventions.

In addition to specifying a time interval, the IRB may specify a subject enrollment number as a threshold for determining when continuing review is to occur. For example, at the time of initial review and approval of a high-risk clinical trial, the IRB might require that continuing review occur either in 6 months or after 5 subjects have been enrolled, whichever occurs first.

The IRB must communicate the project's expiration date to the PI in writing. In addition, the IRB should have policies and procedures in place to assure sufficient time for the PI to submit the continuing review documents, for the IRB to review them, and to receive approval prior to that expiration date. These procedures may include sending reminders to the PI at intervals prior to the approval expiration date.

2. WHAT MATERIALS MUST THE PI SUBMIT TO THE IRB?

IRBs should have written procedures for continuing review that require investigators to submit the following documents, as applicable, if not already available to the IRB as part of the existing IRB records for the research:

- A brief project summary (this could be included as part of a progress report described in the next bullet, provided as a separate document, or be addressed by referencing other documents made available to the IRB);
- A progress report that includes the following:
 - The number of subjects accrued since the IRB's initial review and the last IRB continuing review approval (if the project has undergone a prior continuing review approval). For multicenter research studies, the number of subjects accrued at the local institution and the number accrued study-wide, if available should be included. It is suggested that IRBs clearly indicate to investigators whether or not progress reports should categorize subjects who undergo screening procedures requiring written informed consent or a waiver of documentation of informed consent as accrued subjects or withdrawn subjects. ORD would not consider subjects who have given informed consent to have screening procedures done for a research project and subsequently were unable to meet the inclusion criteria for continued participation in the project (or met an exclusion criteria) as accrued subjects that should be reported at continuing review. ORD would also not consider these individuals to be subjects who have withdrawn from the study for purposes of reporting at continuing review.
 - 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.
 - A summary of both any unanticipated problems and available information regarding adverse events (the amount of detail provided in such a summary will vary depending on the type of research being conducted and the level of risk; in many cases, such a summary could be a brief statement that there have been no unanticipated problems and that adverse events have occurred at the expected frequency and level of severity as documented in the research protocol, the informed consent document, and investigator's brochure, if applicable).
 - A summary of any withdrawal of subjects from the research since the last IRB review, and the reasons for withdrawal, if known (include those lost to follow-up, voluntary withdrawals, or withdrawals by the investigator).
 - A summary of any complaints about the research from subjects or others since the last IRB review.

- The latest version of the IRB-approved protocol and sample informed consent document(s);
- Any proposed modifications to the informed consent document or protocol;
- For FDA-regulated research, the current Investigator's Brochure, if available, including any modifications; and
- Any other significant information related to subject risk, such as the most recent summary from any DSMB or DMC monitoring the research, if available. Even when the DSMB or DMC has identified no problems during its review and simply recommended continuation of the research study as designed, it may be useful for the IRB to be informed of this recommendation.

3. WHAT DOES THE IRB REVIEW?

The IRB reviews all of the materials submitted and determines if any of the material reviewed would change the determination that all criteria for approval have been met with the working presumption that the research, as previously approved, continues to satisfy all of the approval criteria:

- Risks to subjects are minimized (i) by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes;
- Risks to subjects are reasonable in relation to anticipated benefits, if any, to the subjects and the importance of the knowledge that may reasonably be expected to result;
- Selection of subjects is equitable;
- Informed consent will be sought from each prospective subject or the subject's legally authorized representative, and appropriately documented in accordance with, and to the extent required by, VHA Handbook 1200.05;
- When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects;
- When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data;
- Appropriate safeguards are included to protect subjects likely to be vulnerable to coercion or undue influence; and
- When the research involves pregnant women, fetuses, or neonates; prisoners; or children, the research satisfies the additional requirements for IRB approval.

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

The IRB should review a copy of the sample informed consent document submitted by the investigator to verify that the document contains the most accurate, up-to-date information about the research. If the IRB waived the requirement for the investigator to obtain a signed consent form for some or all subjects, the IRB should assess the accuracy of the content of the information being provided to subjects orally and of any written statement regarding the

research that is being provided to subjects. If there is new information that should be considered a significant new finding, the IRB should determine if this should be added to the consent form and communicated with subjects who have already been enrolled.

It also may be appropriate for the IRB at the time of continuing review to confirm that any provisions under the previously approved protocol for monitoring the research data to ensure safety of subjects have been implemented and that no modifications are needed (e.g., the IRB could require that the investigator provide a report from the monitoring entity described in the IRB-approved protocol).

At the time of continuing review, the IRB should ascertain whether enrollment is consistent with the planned number of subjects described in the IRB-approved protocol. A marked difference between the actual and expected rates of enrollment may indicate an issue with the research project that requires further evaluation. The IRB also needs to consider at continuing review whether the enrollment issues impact potential subject safety issues.

The IRB should review the number of subjects who discontinued their participation and the summary of the reasons for the withdrawals, if known. This information may shed light on issues related to the conduct of the research. For example, a high rate of subject withdrawal secondary to unexpected serious adverse events may indicate that the risks of the research are greater than initially expected. The IRB will need to evaluate whether the IRB approval criteria in 38 CFR 16.111 are still met and/or whether modifications need to be made for continued approval of the research.

4. WHEN CAN THE IRB USE EXPEDITED PROCEDURES FOR CONTINUING REVIEW?

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

In general, a research study that was eligible for initial review under an expedited review procedure (met one of the [expedited review categories](#), and involved no more than minimal risk) will qualify for an expedited review procedure at the time of continuing review. However, IRBs should be aware that a research study previously approved under an expedited review procedure in some circumstances will need to undergo continuing review by the IRB at a convened meeting. For example, the investigator at the time of continuing review may propose changes to the research project that involve the addition of activities that do not fall within the scope of any of the categories of research activities eligible for an expedited review procedure.

Research projects not initially eligible for expedited review may become eligible under the following circumstances:

- A research project previously approved by the IRB at a convened meeting progresses to the stage where all of the remaining human subjects research activities involve no more

than minimal risk to the subjects and fall within the scope of one or more of expedited review categories (2) through (7).

- 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 Where no subjects have been enrolled and no additional risks have been identified; OR Where the remaining research activities are limited to data analysis. (See Expedited Review Category 8)
- Research previously approved by the IRB at a convened meeting that meets the following conditions: (i) The research is not conducted under an investigational new drug application (IND) or an investigational device exemption (IDE); (ii) Expedited review categories (2) through (8) do not apply to the research; (iii) The IRB has determined and documented at a convened meeting that the research involves no greater than minimal risk to the subjects; and (iv) No additional risks of the research have been identified. (See Expedited Review Category 9)

5. WHAT HAPPENS IF THERE IS A LAPSE OF APPROVAL?

The regulations at 38 CFR Part 16 make no provision for any grace period extending the conduct of research beyond the expiration date of IRB approval. 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. If approval expires:

(1) The IRB is responsible for promptly notifying the investigator.

(2) The investigator must:

(a) Stop all research activities including, but not limited to, enrollment of new subjects; analyses of individually identifiable data; and research interventions or interactions with currently participating subjects, except where stopping such interventions or interactions could be harmful to those subjects; and

(b) Immediately submit to the IRB Chair a list of research subjects who could be harmed by stopping study procedures. Within two business days, the IRB Chair, with appropriate consultation with the facility Chief of Staff, determines if subjects on the list may continue participating in the research interventions or interactions.

(3) Once the study approval has expired, the IRB should complete the continuing review as soon as possible after the PI has submitted all required documents. The IRB should document why the lapse in IRB approval occurred, and, if appropriate, any corrective actions that the investigator, institution, or IRB is taking to prevent any such lapse of approval of the project from occurring again in the future.

When continuing review of a research project does not occur prior to the end of the approval period specified by the IRB, IRB approval expires automatically. This is not considered to be a suspension or termination of IRB approval. Therefore, such expirations of IRB approval do not need to be reported to ORO or OHRP. However, 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), the IRB should determine whether such a pattern represents serious or continuing noncompliance that needs to be reported to appropriate institutional officials (see VHA Handbook 1058.01).

REGULATORY AND VHA POLICY REFERENCES:

38 CFR 16, Protections of Human Research Subjects.

VHA Handbook 1058.01, Research Compliance Reporting Requirements.

VHA Handbook 1200.05, Requirements for the Protection of Human Subjects in Research.

OHRP Guidance-- <http://www.hhs.gov/ohrp/policy/continuingreview2010.html>