1. POLICY

Periodic review of non-exempt research is required to reassess the totality of the project and assure that it still meets the approval criteria described in RR 401 – Initial Review, with particular emphasis on the criterion that risks to subjects are being minimized and are reasonable in relation to anticipated benefits to the subjects and the knowledge that is expected to result. The IRB conducts continuing review of research at intervals appropriate to the degree of risk.

Specific Policies

1.1 Interval of Review for Purposes of Renewal

1.1.1 ***Research that is subject to federal oversight or is greater than minimal risk***

For purposes of renewal of the IRB approval period, the IRB must conduct continuing review of research that is subject to federal oversight or that presents greater than minimal risk of harm not less than once per year. "Not less than once per year" (45 CFR 46.109e) means that the research must be reviewed and approved on or before the one-year anniversary of the previous IRB approval date.

If the IRB performs continuing review of the research within 30 days before the expiration of the current approval, the anniversary date will usually be retained as the date by which the next continuing review must occur. When the IRB re-approves an ongoing study after a lapse in approval, it may approve the project for one year and establish a new anniversary date, or approve the project for less than a year to retain the original anniversary date. For each study, the IRB will decide the frequency of continuing review necessary to ensure the continued protection of the rights and welfare of the research subjects.

1.1.2 ***Minimal risk research that is not subject to federal oversight***

For purposes of renewal of the IRB approval period, the IRB will generally conduct continuing review of minimal risk protocols that are not subject to federal oversight at intervals of 3 years. This means that the research must be reviewed and approved on or before the three-year anniversary of the previous IRB review date.

If the IRB performs continuing review of the research within 30 days before the expiration of the current approval, the three-year anniversary date will usually be retained as the date by which the next continuing review must occur. When the IRB re-approves an ongoing study after a lapse in approval, it may approve the project for three years and establish a new anniversary date, or approve the project for less time to retain the original anniversary date. For each study, the IRB will decide the frequency of continuing review necessary to ensure the continued protection of the rights and welfare of the research subjects.

1.1.3 ***Changes that impact approval period***

If a minimal risk protocol that has been given a 3 year approval period changes such that it becomes subject to federal oversight (e.g. addition of federal funding source or FDA oversight is initiated), continuing review will be required at that time and the interval of review may be shortened to meet the requirements described above in section 1.1.1.

1.2 Lapses in Approval

There is no provision for grace periods extending approval for the conduct of the research beyond the expiration date of IRB approval. When continuing review and approval does not occur on or before the expiration date, approval expires and the investigator must suspend research activities, including participant recruitment, enrollment, data collection and/or analysis unless it is determined to be in the best interests of enrolled subjects to continue participating in the research. New subjects cannot be enrolled in a study for which approval has expired.

Continuing participation of already-enrolled subjects in research during the period when IRB approval has lapsed may be appropriate when, for example, withholding of the research interventions poses an increased risk to the subjects or when the interventions hold out the prospect of direct benefit to the subjects. The determination of whether it is in the subjects' best interests to continue in the research may initially be made by the investigator. For clinical research, this determination should be made in consultation with the subjects' treating physician, when appropriate. If the investigator finds that it is in the best interests for one or more subjects to continue the research interventions, he or she must inform the IRB as soon as possible and request confirmation of agreement per RR410 – Protocol Deviations and Noncompliances. The determination that it is in their best interest to continue participation may be made for enrolled subjects as a group or for individual subjects.

1.3 Criteria for Renewal

Continuing review must be substantive and meaningful. When considering whether or not to renew approval of a study, the IRB must minimally determine that the criteria used to grant initial approval (see RR 401 – Initial Review) have been satisfied. The IRB starts the review with the presumption that the research, as previously approved, satisfied these criteria and focuses on any new information that would alter the IRB's prior determinations.

1.4 Continuing Review Process

1.4.1 Continuing review application – The investigator must submit to the IRB a complete continuing review application that includes:

- An updated protocol, if amended;
- A current informed consent document and any newly proposed or modified consent document;
- The number of subjects entered to date and since the last review;
- A summary of adverse events and any unanticipated problems involving risks to subjects or others and any withdrawal of subjects from the research or complaints about the research since the last IRB review;

- A summary of any interim findings since the last review;
- Any recent scientific literature or other relevant information that has come to light and might affect the risk/benefit ratio for subjects or their willingness to participate in the research.
- Any relevant multi-center trial reports; and
- New financial conflict of interest disclosure(s).

1.4.2 Consent document – The IRB shall review the consent document and ensure that the information is still accurate and complete. Any significant new findings that may relate to the subject's willingness to continue participation must be provided to the subject in accordance with regulations set forth at 45 CFR 46.116(b)(5). Review of currently approved or newly proposed consent documents *must* occur during the continuing review of the research by the IRB, but informed consent materials should be reviewed whenever new information becomes available that would require modification of the consent document.

1.4.3 Current approved protocol – A copy of the protocol including any previously approved modifications will be sent to at least one member of the IRB (the primary reviewer) of the continuing review. Upon request, any member of the IRB will also have complete access to the protocol file and relevant minutes prior to or during the convened meeting.

1.4.4 Amendments – Any changes to a research protocol should be submitted to the IRB for review as generated during the course of the study. They may also be submitted at the time of continuing review. A description of the change(s) and all appropriate/relevant documentation must be included in the continuing review application.

1.4.5 Continuing review of clinical trials monitored by a Data and Safety Monitoring Board (DSMB) – When a clinical trial is subject to oversight by a DSMB whose responsibilities include review of adverse events, interim findings, and relevant literature (e.g., DSMBs operating in accordance with the National Cancer Institute Policy for Data and Safety Monitoring of Clinical Trials), the IRB conducting continuing review may rely on a current statement from the DSMB indicating that it has reviewed study-wide adverse events, interim findings, and any recent literature that may be relevant to the research, in lieu of requiring that this information be submitted directly to the IRB. However, the IRB must still receive and review reports of local, on-site unanticipated problems involving risks to subjects or others and any other information needed to ensure that its continuing review is substantive and meaningful.

1.4.6 Mode of review – A protocol that was originally reviewed using the expedited review procedure may receive its continuing review on an expedited basis unless the protocol has changed or will change such that expedited review would no longer be appropriate. Conversely, an expedited review procedure may be used for the continuing review of research previously approved by the convened IRB in limited circumstances as described by expedited review categories (8) and (9) (see RR 402 – Expedited Review).

1.4.7 Approval with conditions – When approving research with conditions at the time of continuing review, the IRB will specify whether any conditions need to be satisfied before an investigator can continue particular research activities related to those conditions.

1.4.8 Using a different IRB to conduct continuing review – In general, the IRB that conducted the initial review of a research project will conduct the continuing review. If the need should arise, another IRB may conduct continuing review of the project, but only if its members have the appropriate experience and expertise as well as access to all prior relevant IRB records.

1.5 Significant New Findings

The IRB may review reports generated from a DSMB, adverse event reports, current literature, and other sources to ascertain the status of the study and assess whether or not the risk/benefit ratio is still acceptable. The IRB will also determine whether or not new information needs to be conveyed to subjects, if a segment of the population may be bearing an undue burden of research risk, or a segment of the population is being denied access to promising therapy.

1.6 Study Completion

Continuing review is required as long as a research study continues to involve human subjects. A study is considered to involve human subjects if any of the following activities are ongoing:

(i) research-related interactions or interventions with human subjects;

(ii) collection or receipt of identifiable private information or biological specimens; and

(iii) analysis of identifiable private information or biological specimens.

Once all of the above activities as described in the IRB-approved protocol are finished, then the research study is considered complete and the investigator is no longer required to obtain continuing review and approval for that study by the IRB.

2. SCOPE

These policies and procedures apply to all non-exempt research submitted to the IRB.

3. RESPONSIBILITY

The investigator is responsible for fulfilling requirements associated with the renewal process in sufficient time for the IRB to carry out continuing review of the research before current approval expires.

The OPHS Director (and/or IRB Manager) is responsible for establishing the processes for conducting ongoing reviews of research.

The IRB Chair/Designee is responsible for preliminary assessments of adverse events, significant new findings and the need for third party verification.

4. PROCESS OVERVIEW

Continuing Review – Courtesy Reminder

The expiration date of the approval period is clearly listed on the approval letter for each protocol. It is the investigator's responsibility to keep track of the expiration date and initiate the renewal process in sufficient time for the IRB to conduct the review before current approval expires. However, as a courtesy, the protocol software is designed to send the

investigator automatic email reminders at 60 days, 30 days and 15 days in advance of the expiration of IRB approval.

If a continuing review application is not received and the approval period expires, a software generated automatic email notice will be sent to inform the investigator to stop all research activities, including recruitment and enrollment of research subjects.

Continuing Review - Expedited

In general, when a continuing review application/renewal request that qualifies for expedited review is submitted, OPHS staff will facilitate the review process and perform a preliminary review of the submission. If additional documentation or information is necessary, the responsible staff member initiates correspondence to the investigator.

When the investigator responds, the staff member verifies that all items have been addressed and the application is complete. The application and response are then routed to the IRB Chair/Designee, at which point he or she will review the research. If any concerns are identified, the Chair/Designee will return the application along with his or her comments to the staff member who will communicate these comments to the investigator in writing. If there are no concerns, or when the concerns have been addressed, the IRB Chair/Designee will grant approval.

After the continuation/renewal application is approved, all approved informed consent, parental permission, and assent documents (English and foreign language) will be made available to the investigator along with the protocol approval letter. Any foreign language translations of approved consent documents must be submitted, either with initial application materials, as responsive materials to a conditional approval by the IRB, or as an amendment after initial approval of the research and English consent documents.

If there are any issues that cannot be resolved or if the Chair/Designee determines that the application does not meet the criteria for review by expedited procedures, the application must go to the full committee (convened IRB) for review; the IRB Chair/Designee cannot disapprove a study via the expedited review process.

Continuing Review – Full Committee

When a continuing review application/renewal request that requires review by the convened IRB is submitted, it is generally added to the agenda of the next meeting of the appropriate committee. A staff member will conduct a preliminary review and prepare a written evaluation of the protocol identifying administrative and regulatory issues. Staff then forward the application and the evaluation to all IRB Members per FO 303 – IRB Meeting Administration. If a research project requires special consideration or expertise, the OPHS Director, IRB Manager, or IRB Administrator arranges for a consultant's participation and the necessary documentation is forwarded to the special consultant.

At the IRB meeting, the primary reviewer (and/or secondary reviewer) presents the study responding to the staff member's evaluation and elaborating on any aspect of the study he or she deems appropriate to discuss. Other members may ask questions and engage in discussion regarding the protocol. The IRB may approve the renewal request, disapprove continuation of the research, require minor revisions (conditional approval), or defer consideration to another convened meeting (see RR 407 – Categories of Action). The investigator is notified of the review outcome in writing. If minor revisions or clarifications are required, the IRB will designate an individual with appropriate expertise to review the investigator's response in order to verify that the conditions for approval have been satisfied.

However, if the IRB determines that the concerns/revisions are substantive, the investigator's responsive materials will be sent to another convened meeting for consideration.

After the continuation/renewal application is approved, all approved informed consent, parental permission, and assent documents (English and foreign language) will be made available to the investigator along with the protocol approval letter. Any foreign language translations of approved consent documents must be submitted, either with initial application materials, as responsive materials to a conditional approval by the IRB, or as an amendment after initial approval of the research and English consent documents.

If the IRB does not re-approve the research, a staff member will send the investigator a letter (per RR 409 – Suspension or Termination of a Protocol) identifying the reason for the suspension or termination.

5. APPLICABLE REGULATIONS AND GUIDELINES

45 CFR 46.109

21 CFR 56.109

45 CFR 46.111

21 CFR 56.111

45 CFR 46.110

21 CFR 56.110

Federal Register Volume 63, No 216

45 CFR 46 Subparts B, C & D

OHRP Guidance on IRB Continuing Review of Research (Nov 2010)

The Belmont Report