Sheet 9: CONTINUING REVIEW OF RESEARCH INVOLVING HUMAN SUBJECTS

1. INTRODUCTION

At the NIH, research activities involving human subjects must be reviewed and approved by an Institutional Review Board (IRB) before they begin. In addition, IRBs are required by Federal regulation to conduct continuing reviews of research at intervals appropriate to the degree of risk, but not less than once a year, in order to reassure themselves, investigators, research subjects, and the public that appropriate measures are being taken to protect the rights and welfare of human research subjects.

Continuing review and approval must be completed by the continuing review date otherwise IRB approval for the protocol expires. Research may not be conducted absent IRB approval. Research activities involving identifiable human specimens and identifiable data must occur under an open protocol, either the protocol which is the source of the specimens and data, or another NIH protocol. Federal regulations and NIH policy do not provide for exceptions to the requirement for continuing review, therefore failure by the Principal Investigator (PI) to ensure timely IRB review is a serious matter that may lead to termination of the protocol.

2. CONTINUING REVIEW REQUIREMENTS

The criteria used by IRBs to evaluate research activities are found in the NIH Manual Chapter 3014,"NIH Human Research Protection Program," and the NIH Standard Operating Procedures for IRBs, Chapters 5 and 6.

Continuing reviews by NIH IRBs must be substantive and meaningful. To ensure an informed judgment, all IRB members must receive, at a minimum, the completed NIH 1195-1, the investigator's summary and the current consent document(s). At least one member must receive the complete protocol. When the review takes place in a convened IRB meeting, the protocol must be approved by a majority of the members present. The IRB's stipulations, if any, and any other requirements, such as Radiation Safety Committee clearance and required signatures, must be met by the continuing review due date before approval for continuation may be granted.

The research use of coded samples/data (when researchers maintain the ability to identify subjects) must be conducted on an IRB-approved protocol and receive continuing review.

Research protocols that require full IRB review for their initial reviews generally require it for their continuing reviews. The expedited review process may be used when: (1) the protocol is permanently closed to enrollment of new subjects, all subjects have completed all research-related interventions, and the research remains active only for long-term follow-up of subjects; or (2) where no subjects have been enrolled and no additional risks have been identified; or (3) where the remaining research activities are limited to data analysis (See NIH Standard Operating Procedures for IRBs, Attachment 5-8, Expedited Review Categories).

3. DOCUMENTATION REQUIRED BY THE IRB FOR THE CONTINUING REVIEW

The Principal Investigator (PI) is responsible for timely submission of the continuing review application to the appropriate NIH IRB. Minimum required documentation is:

- A completed NIH 1195-1 ("Clinical Research Protocol Continuing Review Application");
- The protocol, with version and page numbers, and consolidation of all amendments since its last review;
- Up-to-date protocol consent document(s);
- Any additional IC requirements (e.g., checklists) and
- A summary report addressing the following: (1) a brief narrative explaining current progress/findings from the research; (2) a summary of any amendments made to the research protocol since the last review; (3) the number of subjects accrued, including a demographic table meeting the criteria set forth in Information Sheet 11, "INCLUSION OF WOMEN AND MINORITIES IN STUDY POPULATIONS: GUIDANCE FOR IRBs AND PRINCIPAL INVESTIGATORS". (See also attachment 6-6b {Inclusion Enrollment Report} of the NIH Standard Operating Procedures for IRBs); (4) a summary of adverse events and any unanticipated problems involving risks to subjects or others; (5) a summary of subject withdrawals from the research; (6) any reports of complaints about the research since the last IRB review; (7) any relevant multi-center reports; (8) any data and safety monitoring board reports; (9) any information from the literature or from this or similar research that might affect the IRB's evaluation of the risk/benefit analysis of human subjects involved in this protocol; and (10) reason(s) for continuing the study;
- A summary of the FDA annual report, if applicable.

Continuing review applications that do not include these documents will not be accepted for review by an NIH IRB.

4. TIMING OF THE CONTINUING REVIEW SUBMISSION TO THE IRB

Unless the IRB specifies a shorter time period, continuing review must be completed within 1 year from the date the protocol was last approved by the IRB. The Clinical Center's Office of Protocol Services (OPS) sends to the PI two reminders of the due date; the first is sent 120 days and the second is sent 60 days before the continuing review due date.

The PI must submit the necessary documentation to the appropriate NIH IRB office in sufficient time to permit completion of the IRB review and approval process before the due date. Depending on the IRB meeting schedule, submissions may be required from 45-60 days before the regularly scheduled IRB meeting.

5. EXPIRATION OF IRB PROTOCOL APPROVAL

In keeping with federal regulations, the NIH expects all protocols to complete IRB review and approval by their continuing review due date. IRBs and PIs must plan ahead to meet required continuing review dates. If by the specified review date the IRB has not completed its review and approval, the IRB approval for the study expires. Upon expiration, enrollment of new subjects cannot occur and all research activity, including subject follow up, study interventions, and data collection and analysis must stop. In the extremely rare circumstance when 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 study activities to continue for the brief time required to complete the review process.

Within 24 hours of expiration of IRB approval, the OPS will block accrual of new subjects. An e-mail notification of this action will be sent to the PI, IRB Chair, IRB office, OHSR and the IC Clinical Director. This notice and all correspondence about an overdue protocol from the OPS and the IRB will be maintained in the PI's protocol file and in the IRB office.

6. TERMINATION OF THE PROTOCOL

Protocols that have not been submitted for review to the IRB by their expiration date are automatically terminated. Protocols which have been reviewed by the IRB by their expiration date but which have not completed their approval within 30 days of notification of expiration are terminated by the IRB. The PI, IC Clinical Director, OHSR, OPS, and the Director of the Clinical Center will be notified of such action. Upon notification of termination, the PI must submit to the IRB proposed procedures for withdrawal of currently enrolled subjects that takes into consideration their rights and welfare. Reactivation of a terminated study requires submission of a protocol to the IRB for initial review.

7. SETTING THE CONTINUING REVIEW DUE DATE

The protocol continuing review date is set according to the date of approval by a convened IRB. If the PI's responses to the IRB's stipulations require for approval simply a concurrence by the IRB Chair or his designee, the continuing review date is the date of the convened meeting where the stipulations were assigned. If the IRB requires the PI's stipulation responses to be reviewed by the full IRB, the continuing review date is the date of final approval by the convened Board. Continuing review dates may fluctuate from year to year based on the date of the convened IRB meeting when approval was granted.