1.0 Purpose

To assure knowledge and compliance by documenting the continuing review procedure of approved projects for the Health Sciences IRB.

2.0 Scope

The SOP applies to all human subject research falling under the purview of the Health Sciences Institutional Review Board.
3.0 Policy/Procedure

Continuing review of research must be substantive and meaningful. Continuing review by the convened IRB, with recorded vote on each study, is required unless the research is otherwise appropriate for expedited review under 45 CFR 46.110.

Regulations codified at 45 CFR 46.111 set forth the criteria that must be satisfied in order for the IRB to approve research. These criteria include, but are not limited to, determinations by the IRB regarding risks, potential benefits, informed consent, and safeguards for human subjects. Not only must the IRB ensure that these criteria are satisfied at the time of initial review, but also at the time of continuing review.

Requirements

At the time of initial review and approval of a research proposal, the Board establishes a time interval by which continuing review of the project must occur. This interval can be set for any length of time but must be no longer than 12 months from the initial approval or continued approval date. The determination regarding the appropriate review intervals will be made based on considerations of the potential or actual risks of the research, the degree of novelty of the research intervention, the number of subjects to be enrolled, any specific vulnerability associated with the research population, and/or the magnitude or frequency of risk to subjects. The Board may request a separate review or change the review interval at any time they deem it necessary because of revised information from an amendment, unanticipated problem, or information obtained during a scheduled continuing review.

Criteria for Review Schedule:

- Studies may be reviewed more frequently than annually if the IRB believes that the study population is especially vulnerable.
- Studies may be reviewed more frequently if the IRB believes that previous studies of a similar nature indicate a high incidence of unanticipated problems.
- Studies may be reviewed more frequently if the IRB believes that closer monitoring is needed based on the review of materials provided.
- If the IRB determines that a study that has been approved for an annual review requires closer monitoring, the IRB may make a determination to review the study on a more frequent basis. The reasons for such a determination will be included in the minutes and communicated to the investigator.

Principal Investigators will be informed in the project approval letter of the scheduled continuing review interval for the project. It is the responsibility of the Principal Investigator to submit the CRR even without notification from the HS IRB office. Continuing review is mandatory for all currently active research projects; including those that have been closed to subject accrual but are still involved in data collection and analysis or are in long-term follow-up.

The information requested on the Continuing Review Report (CRR) includes:

- Description of current consent process
- Verification that informed consent and assent (if required) was obtained from all subjects and that all signed consent (assent) forms are on file (unless requirements have been waived)
• Verification that consent form has not been translated without IRB approval
• Current project status, if the study is closed to enrollment, the date that the study closed to enrollment
• Current funding source and status
• Approved target enrollment; study-wide and on-site
• Number of subjects enrolled on-site (since original approval and since last continuing review
  o Breakdown of information into number of subjects consented, number of subjects that withdrew from the study, number of subjects currently on active treatment or long term follow-up, number of subjects who have completed the study, number of subjects whose participation was terminated by the investigator, number of subjects lost to follow-up
• Enrollment information for VA subjects to include the number enrolled, gender and minority status of each participant, the number of participants considered as members of specific vulnerable populations
• Reasons for withdrawal of participation
• Reasons for termination of subjects
• Current progress of enrollment
• Subject complaints
• Special subject population information
• Accrual information for chart reviews, database reviews and specimens
• Brief narrative of study summary
• Investigational drug information
• Standard of care information
• Subject compensation information
• A description of any change in cost to the participant
• Number and description of any Unanticipated Problems
• Number of Amendments
• Description of Amendments
• Change in study personnel
• Any changes in the study that may affect the privacy of participants and confidentiality of data
• A summary of any participant benefits
• Progress of research
• Changes in literature
• Description of preliminary findings
• Data safety monitoring information and reports
• Sponsor Monitoring information and reports
• Federal Agency audit information and reports
• Certificate of Confidentiality information and report
• If multi –center study and lead institution or lead investigator, describe the management and communication of information obtained
• Conflict of Interest Disclosure

All CRRs will be acted upon by the full board unless they meet the expedited review requirements as codified in 45 CFR 46.110 (please see section on Expedited Review for additional information). All continuing reviews will be conducted using a primary reviewer system of review.
The IRB will determine that the risk to subjects continues to be minimized and will systematically consider physical, social, economic, legal and psychological risks. In evaluating risks and benefits, the IRB will consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies that subjects would receive even if not participating in the research).

**Changing the Status of a Study on a CRR form**

A CRR form may be used to change the status of a study yearly as necessary. If a study is “Active-open to enrollment” one year, but over the course of the following year, has changed to “Closed-data analysis only,” this change should be reflected on the CRR.

If a study has been completed, but a Completion/Termination/Withdrawal Form has not yet been submitted at the time of study expiration, a CRR form must be submitted in lieu of the Completion Form. This eliminates the confusion often caused by submitting a Completion Form at CRR time and expedites the approval of the form.

**Submission**

A query is run on the first working day of the month for all studies where the approval expires two months later. EXAMPLE: On April 1, 2004, a query is run to find all studies where the approval expires in June 2004. From this query the first notice of expiration is sent to the Primary Contact for the study and a CRR form is made available in the electronic submission system for completion. It is the responsibility of the Principal Investigator to submit a CRR even without notification from the HS IRB office.

The deadlines for continuing review are on the website and listed in the notification sent to the primary contact and/or the primary contact and investigator. The notification also details the last possible date that the CRR can be received in the IRB office before the study will expire. This due date is measured in terms of the last convened board meeting prior to the study’s approval expiration. In order to be reviewed at a particular board meeting, the CRR must be submitted no later than three weeks prior to the board meeting for adequate preparation for review. EXAMPLE: The approval for a study expires on May 3, 2004. The last board meeting at which this study can be approved is April 28, 2004. Three weeks before this board meeting is April 7, 2004. Therefore, the last possible date that the CRR can be submitted to the IRB office is April 7, 2004. If the CRR has not been submitted by the due date, the study will expire on its expiration date. In rare occasions, CRRs submitted after the final due date are looked at on a case-by-case basis to determine if there is adequate time to prepare the CRR for review.

A complete CRR submission consists of one copy of each of the following where applicable:

1. Completed CRR form
2. Clean copy of the consent form (VA consent form and/or assent, if applicable) – if the study is active, open to enrollment
3. Complete copy of current protocol (if not already on file)
4. Copy of CIDB (if not already on file)
5. Group Meeting Information (CALGB, GOG, ASCOG, COG, etc.)
6. Data Safety & Monitoring Information or Reports
7. Grant application – if not previously submitted
8. Certificate of Confidentiality
9. Statement of Compliance
10. Sponsor monitoring reports
11. Sponsor progress report
12. VA R&D approval form
13. Audit reports from Federal agencies or other reviewing entities
14. MU and/or Sponsor Conflict of Interest disclosure form
15. Any relevant literature
16. Any relevant multi-center trial reports
17. Other supporting documentation

Numbers 2-15 are considered “attachments” by the HS IRB office and will be referred to as such throughout this SOP.

**Processing and Review**

The IRB office staff review each CRR for accuracy, completeness and whether it qualifies for full board or expedited review. Any questions or clarifications on the project status, progress report, enrollment, etc. are handled via communication with the Principal Investigator or Study Coordinator. All CRR forms will be acted upon by the full board unless they meet the expedited review criteria as codified in 45 CRF 46.110.

**Expedited Review**

Applicability:

- Research eligible for initial review by an expedited procedure. (See initial review policy)
- Research that meets the criteria codified in 45 CFR 46.110 (8-9) may be expedited.

8) Continuing review of research previously approved by the convened IRB as follows:
   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.

9) Continuing review of research, not conducted under an investigational new drug application or investigational device exemption where categories two (2) through (8) do not apply but the IRB has determined and documents at a convened meeting that the research involves no greater than minimal risk and no additional risks have been identified.

For a multi-center protocol, an expedited review procedure may be used by the IRB at a particular site whenever the conditions of category (8)(a), (b), or (c) are satisfied for that site. However, with respect to category 8(b), while the criterion that "no subjects have been enrolled" is interpreted to mean that no subjects have ever been enrolled at a particular site, the criterion that "no additional risks have been identified" is interpreted to
mean that neither the investigator nor the IRB at a particular site has identified any additional risks from any site or other relevant source.

Expedited continuing reviews will be conducted using a primary reviewer system of review. As each CRR form is received and categorized as expedited, it will be assigned to a primary reviewer for review (typically the IRB chairs for expedited reviews). The primary reviewer will receive the same information, when applicable, as provided in a full board continuing review. Upon request to the IRB staff, the reviewer may have access to the complete IRB protocol file and relevant IRB minutes prior to or during the convened IRB meeting. The primary reviewer may determine that the CRR does not qualify for expedited review and must be reviewed by the convened Board. If the reviewer disapproves the expedited continuing review, the study will be put on the next full board meeting agenda. The investigator will be notified in writing. The Board will be notified through attachments to the agenda of all CRRs that were reviewed at the expedited level.

- In conducting continuing review, the reviewer must determine that all applicability criteria are met and that all research activities fall into one or more categories of research allowing review by the expedited procedure.
- When granting continuing approval the reviewer must document the category allowing review by the expedited procedure.
- Documentation should include any actions taken by the reviewer and any findings required under the regulations.
- The reviewer may request specific revisions requiring simple concurrence by the investigator or minor modifications or clarifications as defined in this policy. These revisions may be processed administratively and reviewed by the Chair or other designee.

Full Board Review
The continuing reviews will be conducted using a primary reviewer system of review. As each CRR form is received, it will be assigned to a board meeting using the thirty (30) day window allowed by OHRP. Each CRR will also be assigned to a primary reviewer for review by the IRB staff. The IRB staff will ensure the primary reviewer has the appropriate expertise. The IRB staff will address conflicts of interest as described in the Conflict of Interest Policy. The Primary Reviewer (and all other board members) will have access to the following information at least 5 working days prior to the scheduled IRB meeting:

- Completed CRR form (status report) and all attachments; to include:
- The number of subjects accrued;
- Copy of current protocol including any modifications previously approved by the board
- Original approved application
- Detailed Project History report
- Unanticipated Problem Log (if applicable)
- Amendment Log (if applicable)
- A copy of the current informed consent document/assent document
• A summary of 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 relevant recent literature, interim findings, and amendments or modifications to the research since the last review;
• A summary of any participant benefits since the last IRB review.
• Any relevant multi-center trial reports;
• Data safety monitoring information, monitor reports and study progress reports
• Relevant IRB minutes
• Any other relevant information, especially information about risks associated with the research.

The primary reviewer is expected to review these materials in depth and complete the continuing review checklist. Reviewers are required to ensure that the submitted informed consent documents and protocols are accurate and complete. Any significant new findings that may relate to the subject's willingness to continue participation should be provided to the subject in accordance with HHS regulations at 45 CFR 46.116(b)(5). Other board members are expected to have a working knowledge of all submitted materials for the continuing review and be able to engage in a meaningful discussion of the project.

Additional Review Requirements
Several other reviews are necessary for studies involving prisoners, devices, drugs, accounting, conflict of interest, veterans, and radiation or biosafety. These reviews take place during initial review of the study or an amendment. However, additional information will be provided, as needed, regarding prisoners, devices, drugs, accounting, conflict of interest, veterans, and radiation or biosafety, to ensure a substantive and meaningful continuing review in accordance with HHS regulations at 45 CFR 46.108(b) and at 46.115(a)(2).

Some information may not be readily available to investigators participating in multi-center clinical trials. Such trials are often subject to oversight by a Data and Safety Monitoring Board (DSMB), Data Monitoring Committee (DMC), other similar body, or sponsor whose responsibilities include review of adverse events, interim findings, and relevant literature.

If a study is subject to oversight by a Data and Safety Monitoring Board (DSMB), the IRB may rely on a current statement from the DSMB or sponsor 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. The IRB must still receive and review reports of unanticipated problems involving risks to subjects or others (which would include adverse events that are deemed reportable under HS IRB policy) and any other information needed to ensure that its continuing review is substantive and meaningful. The IRB may require additional information for continuing review at their discretion.
If any of the following are true, the IRB will generally get verification from sources other than the investigator that no material changes have occurred since the previous IRB review:

- The investigator has a history of serious or continuing non-compliance related to continuing review in the past three years.
- The IRB has reasons to doubt the veracity of the information provided by the investigator.
- The information provided by the investigator is inconsistent with other information known to the IRB and the inconsistency cannot be resolved through communication with the investigator.
- Any other reason where the IRB believes that verification should be required.

The primary reviewer will present to the Board any problems or questions found during the continuing review. Also, any Board member may indicate for discussion any issues they found during their review of the CRR. The minutes of IRB meetings will document separate deliberations, actions, and votes for each protocol undergoing continuing review by the convened IRB.

**Actions**

If no issues are raised the project will be approved to continue for another year (or whatever the originally indicated approval period).

Specific revisions stipulated by the convened IRB requiring simple concurrence by the investigator or minor modifications or clarifications* as defined below may be reviewed using the expedited procedure.

*Minor Modifications or clarifications:

- Those modifications or clarifications that do not involve potential for increased risk or decreased benefit to the human subjects.
- Protocol revisions that entail no more than minimal risk to participants are considered “minor” modifications.
- Changes to informed consent documents that do not affect the rights and welfare of study participants, or do not involve increased risk, or significant changes in the study procedures
- New or revised recruitment advertisements or scripts.

The IRB administrative office will request the clarifications or revisions from the investigator in writing. This request and the written response will be documented in the file. The IRB staff will review for completeness, the clarifications or documented changes when they are received. The clarifications are subsequently reviewed and approved by the IRB chair or another designee in a timely fashion.

When the convened IRB requests substantive clarifications or modifications regarding the protocol or informed consent documents that are directly relevant to the determinations required by the IRB for research under 45 CFR 46.111, the convened IRB must review the revisions. The board will try to contact the investigator by phone and ask the investigator to come to the meeting for discussion or have a discussion by speaker phone. If the investigator is not available the board will defer review of the CRR and the
modifications will be requested of the investigator by the IRB office in writing. Enrollment of new subjects will be revoked immediately or at the time current approval expires, and remain revoked until final re-approval is granted. The committee may allow continuation of study interventions/procedures pending final re-approval. The request and response will be documented in the file. The project will be re-reviewed with the written documented modifications at the next convened board meeting to determine approval status. The investigator may request to attend the meeting to discuss the study under review and answer questions or provide explanation. In addition, the board may request that the investigator attend the meeting to address concerns of the study.

If the issues raised are substantial enough to warrant Board concern that the risks/benefits ratio has been altered and if the opinion of the Board it is necessary, the Board may disapprove the continuation of the project. At the board’s discretion, an attempt to reach the Principal Investigator will be made to address the concerns at the current meeting.

If the IRB deems that the study is not being conducted in accordance with requirements, or a change has occurred in the risk/benefit ratio necessitating termination of the approval, the Principal Investigator will be promptly notified with written justification. The letter will include the reason(s) for disapproval and recommendations, if any, on how to proceed. The investigator will be given the opportunity to respond. (see appeals policy)

**CRR approval**

Once continuing approval has been granted the IRB Chair, indicating the date of review, the date of approval, and the approval expiration date, will sign the completed CRR. When the continuing review occurs annually and the IRB performs continuing review within 30 days before the IRB approval period expires, the IRB may retain the anniversary date as the date by which the continuing review must occur. The new expiration date is calculated from the last approval date plus 12 months (or other time frame as specified by the Board).

EXAMPLE: A CRR was reviewed by the convened IRB on April 14, 2004 and it expires on May 10, 2004. The review date would be April 14, 2004. The approval date would be May 10, 2004 and the approval expiration date would be May 10, 2005.

This review and approval system is in accordance with the guidelines set forth by OHRP on July 11, 2002.

Failure to return the completed CRR or to inadequately complete the CRR prior to the deadline set by the IRB office may result in expiration of the study on its expiration date. The Principal investigator will be notified first via email, then in writing by the IRB, when the project has expired.

**Approval Expiration**

The IRB and investigators must plan ahead to meet required continuing review dates. If an investigator has failed to provide continuing review information to the IRB or the IRB has not reviewed and approved a research study by the continuing review date specified by the IRB, the research must stop, unless the IRB finds that it is in the best interests of individual subjects to continue participating in the research interventions or interactions. The IRB Chair will notify investigators (including VA investigators if applicable) to
immediately submit to the IRB, a list of participants for whom stopping research activities would cause harm. Enrollment of new subjects cannot occur after the expiration of IRB approval. The regulations make no provision for any grace period extending the conduct of research beyond the expiration date of IRB approval. Investigators are required to promptly report the expiration to the sponsor.

For studies involving the VA, all research activities must stop unless the IRB or IRB chair, in consultation with the VAMC Chief of Staff, found that it was in the best interests of individual participants to continue in the study.

When continuing review of a research protocol does not occur prior to the end of the approval period specified by the IRB, IRB approval expires automatically. Such expiration of IRB approval does not need to be reported OHRP as a suspension of IRB approval under HHS regulations.

If a study has been prematurely completed, a Completion/Termination/Withdrawal Form should be completed and submitted to the IRB as soon as possible. If a Completion/Termination/Withdrawal Form has not yet been submitted at the time of study expiration, a CRR form must be submitted in lieu of the Completion Form. This eliminates the confusion often caused by submitting a Completion Form at CRR time and expedites the approval of the form.