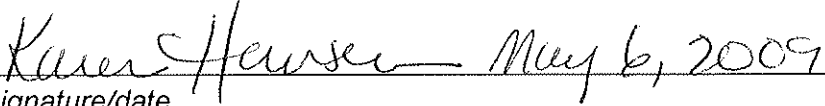


Title:	Continuing Review
Responsible Office:	Institutional Review Office (IRO)
Responsible Official:	Karen Hansen, IRO Director
	 Signature/date
Effective Date:	May 15, 2009
Policy:	2.2

POLICY STATEMENT

It is the policy of Fred Hutchinson Cancer Research Center (FHCRC) that IRB continuing review of approved research studies must occur based on the degree of risk of the study and will never be more than one year from the IRB review date unless the study is Exempt. The review will be in accordance with federal regulation using either an expedited review process; or a convened review process. The *Continuation Review Report Form (CRR)* must contain information to allow the IRB to determine that the research may continue, should be modified, or should be terminated.

DEFINITIONS

Minimal Risk: A risk is minimal where the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests. [45 CFR 26.102 (i)] For example, the risk of drawing a small amount of blood from a healthy individual for research purposes is no greater than the risk of doing so as part of routine physical examination.

Exempt: Activities that are broad categories of research that are "exempted" from IRB review and meet conditions detailed in 45 CFR Section 46.101(b) or 21 CFR 56.104 and may not be protocols involving prisoners.

Expedited Review: The review of proposed research by the IRB chair or a designated voting member or group of voting members (i.e. subcommittee) rather than entire convened IRB. Federal rules permit expedited review for certain kinds of research involving no more than minimal risk and for minor changes in approved research [Federal Policy §____.110] Category (8) (a), (b), (c), Category (9)].

Full Board Review: Review of proposed research at a convened meeting at which a majority of the membership of the IRB are present, including at least one member whose primary concerns are in nonscientific areas. For the research to be approved, it must receive the approval of a majority of those members present at the meeting [Federal Policy §____.108].

REFERENCES

56 CFR 113
45 CFR 46.109(d)(e)
45 CFR 46.111
45 CFR 46.103(b)(4)(i)(ii)
45 CFR 46.116(b)(5)
21 CFR 50.25(b)(5)
21 CFR 56.103(a)
21 CFR 56.108(a)(1)(2)(4)
21 CFR 56.108(a)(4)
21 CFR 56.108(a)(3)
21 CFR 56.108(b)(2)
21 CFR 56.109(d)(f)
21 CFR 56.111
38 CFR 16.103(b)(4)(i)(ii)

OHRP Compliance Guidance on Continuing Review

OHRP Compliance Activities: Common Findings and Guidance #5; #7; #16; #65;
#71(a)(b)(c)(e)(g)(k); #72

FDA Information Sheets: Continuing Review After Study Approval, Frequently Asked Questions:
IRB Records

FDA Information Sheets: Frequently Asked Questions: IRB Procedures

PRINCIPLES/OVERVIEW

The purpose of continuing review is to analyze the progress of the entire study and the risk/benefit ratio to ensure continuation of the research is acceptable. 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.

INDIVIDUALS AFFECTED BY THIS POLICY

The contents of this policy apply to IRO staff, IRB members, and FHCRC and University of Washington Consortium investigators. Instructions to investigators are posted on the IRO website.

PROCEDURES

The IRB must conduct substantive and meaningful continuing review of research at intervals appropriate to the degree of risk. The IRB has the authority to monitor the data produced by the study, the consent process, and the research itself either through the IRB office or using independent consultants. Once the period of approval is established, it will be communicated to the Principal Investigator (PI) in writing in the approval documents.

The IRB may determine that significant new findings regarding the research might relate to research participants' willingness to continue taking part in the research. In such cases the IRB has the authority to require provision of such information to research participants.

1. Criteria for Conducting Continuing Review

- a. FDA and DHHS regulations set forth the criteria to be satisfied if an IRB is to approve research. These criteria are the same for initial review and continuing review.
 - the number of research participants accrued;

- a summary of any unanticipated problems and available information regarding adverse events (in many cases, such a summary could be a simple 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 any investigator brochure);
- a summary of any withdrawal of research participants from the research since the last IRB review;
- a summary of any complaints about the research since the last IRB review;
- a summary of any recent literature that may be relevant to the research and any amendments or modifications to the research since the last IRB review;
- any relevant multi-center trial reports;
- any other relevant information, especially information about risks associated with the research;
- a copy of the current informed consent document and any newly proposed consent document;
- a copy of the complete protocol; and
- any modifications previously approved by the IRB since the last approval.

2. Continuation Review Report (CRR) Notification Process

- a. Each PI conducting research involving the use of research participants, in whole or in part, whether the activity is minimal risk or more than minimal risk, will be sent an *Continuation Review Report Notice* approximately ten (10) weeks before their current approval expires. All Institutional Review File Numbers will be retained from previous years.
- b. Upon receipt of a completed *CRR*, IRO staff will screen and forward the materials for review in accordance with this policy.

3. PI Submission Responsibility:

It is the responsibility of the PI to complete the *CRR* and attach all relevant materials to it (e.g. protocol, consent form(s), letter(s) of approach, etc.) The *CRR* and appended materials should be submitted by the specified submission deadline to assure continuation of approval.

4. Process for Conducting Continuing Review

- a. For continuing review the IRB reviews the *Continuation Review Report (CRR)* as a written progress report(s) from the PI.
- b. The IRB reviews a copy of the consent document currently in use and determines whether the information contained in the consent document is accurate and complete. The review will include whether new information that may have been obtained during the course of the approval period needs to be added and if the consent document being used by the PI has current IRB approval.
- c. Continuing review responsibilities also include IRB involvement in reviewing reports of unanticipated problems involving risks to subjects or others which occurred during the course of the study. These events are to be reported to the IRB in a timely manner and in accordance with the IRB's policies as outlined in IRB policy 1.11 *Reporting Obligations for Principal Investigators* and IRB Policy 2.6 *Unanticipated Problems Involving Risks to Subjects and Other*.

Unanticipated risks or new information that may impact on the risk/benefit ratio must be promptly reported to, and reviewed by, the IRB to ensure adequate protection of the welfare of the subjects. Based on such information during continuing review, the IRB may reconsider its approval of the study and the frequency for continuing review.

Section 6.0 Data Collection and Monitoring of the *Continuation Review Report (CRR) Form* outlines the reporting requirements for unanticipated problems and serious or continuing noncompliance.

- d. The continuing review process is in accordance with federal regulations using either:
- i. Full Board Review at a convened IRB meeting as defined above. All IRB members have access to the review materials as described in *Section 9, Checklist of the CRR Form*. When an IRB member is neither the primary or secondary reviewer, h/she is expected to review the *CRR*, most current protocol, consent or assent forms in enough depth to discuss the information at the convened meeting. All IRB members have access to the *IRB Member Checklist* and *IRB Member Consent Process and Documentation Checklist*. Any IRB member may request additional information.

For studies undergoing full board review process as noted above, the PI is responsible for submitting the *CRR* and any relevant documents (e.g., active participant documents) as described in *Section 9, Checklist of the CRR Form*.

- ii. An Expedited Review process as defined in 45 CFR 46.110(a) may be used for the continuing review of research previously approved by the convened IRB as follows:

Category (8) as defined in 45 CFR 46.110(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
- Where no subjects have been enrolled and no additional risks have been identified; or
- Where the remaining research activities are limited to data analysis.

Per Category 9 as defined in 45 CFR 46.110(a), an expedited review process as defined above may also be used if the research is not conducted under an investigational new drug application (IND) or investigational device exemption (IDE) and where the research categories (2) through (8) as defined in 45 CFR 46.110(a) do not apply but the IRB has determined and documented at a convened IRB meeting that the research involves no greater than minimal risk and no additional risks have been identified. For activities meeting Category 9, the *CRR* will be reviewed by the IRB Committee at a convened IRB meeting. The IRB Committee will determine if subsequent review may undergo expedited review.

For studies reviewed via the expedited review process as noted above, the PI is responsible for submitting the *CRR* and any relevant documents as described in *Section 9, Checklist of the CRR Form*. For studies that have completed accrual and now qualify for expedited review per #8 of the *Expedited Review Checklist for Minimal Risk Activities*, a copy of the most recently approved consent form and protocol is sufficient.

5. Review and Deliberation by the Full IRB or by the IRB Chair or Designee via Expedited Review

- a. The IRB independent evaluation using *IRB Member Checklist* will 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. The *Study That May Require IRB Review More Often Than Once A Year* checklist is included in the *IRB Member Checklist* to assist the IRB Committee or the IRB Chair (or designee) to determine the frequency of review.

During continuing review the IRB also considers:

- i. Any unanticipated problems involving risks to research participants
 - ii. Any new information regarding the risk and benefits to the research participants
 - iii. Risks posed by the study intervention
 - iv. The type of safety monitoring is provided in the protocol
 - v. Changes in the risk/benefit ratio.
- b. The IRB may approve research for a defined time period which will be no greater than one year. If additional risks to participants are identified the IRB may approve the research with additional restrictions (e.g. limiting number of research participants enrolled, requiring more frequent reporting to the IRB).
- c. Upon review of the *CRR* the IRB will make one of the following determinations:
- Approved
 - If review by external departments or committees other than the IRB is pending (e.g., Radiation Safety Committee [RSC], Institutional Biosafety Committee [IBC] or Industry Sponsored Contract), status of application is approved, however no study documents (i.e., protocol, consent forms, questionnaire) are released to the investigator.
 - Require modifications
 - Disapproved or Tabled
 - A study is disapproved when the IRB determines that the study requires major modifications and the Principal Investigator's (PI) response requires subsequent full IRB Committee review.
 - A study is typically tabled when there is a loss of a quorum which delays the review of the study until the next convened IRB meeting.
- For a list of minor and major modifications, please see IRB Policy 1.6 *Meeting and Meeting Records*.
- d. For *CRRs* undergoing the expedited review process, the IRB Chair or designee determines that the *CRR* meets one of the expedited review categories as defined above, the IRB Chair or designee may make the following determination:
- Approved
 - If review by external departments or committees other than the IRB is pending (e.g., Radiation Safety Committee [RSC], Institutional Biosafety Committee [IBC] or Industry Sponsored Contract), status of application is approved, however no study documents (i.e., protocol, consent forms, questionnaire) are released to the investigator.
 - Require modifications
 - Request full IRB Committee review - The *CRR* does not meet one of the minimal risk expedited review research categories, the PI will be notified that the *CRR* requires full IRB Committee review.

- e. All *CRRs* which were reviewed under expedited review are reported on the next available committee agenda under the section, "CRR That Have Undergone Expedited Review". IRB members are given an opportunity to request full IRB review or to review additional documents of any items that underwent expedited review.
- f. Consultant: When it is determined that expertise and knowledge are needed that does not exist currently with the IRB membership (e.g. cultural appropriateness, scientific expertise, vulnerable population), consultants are invited to review and provide comments to the IRB Chair or designee. See *IRB 1.3 Policy IRB Committee Structure* for specific information regarding consultants.

6. CRR Review Requirements for Cooperative Review Agreements or IRB Authorization Agreements

- a. Each PI conducting research which requires review by an IRB and which was originally reviewed at another institution under the auspices of an *IRB Cooperative Review Agreement* or *IRB Authorization Agreement*; will be sent a *Continuation Review Report Notice* reminding them of their upcoming expiration. It is the responsibility of the PI to contact the appropriate institution's review office to become familiar with the necessary continuing review procedure.
- b. For both *Cooperative Review Agreement* and *Authorization Agreement*, it is the PI's responsibility to forward to the IRO the following materials at a minimum, once a year:
 - First page of the FHCRC *CRR*;
 - IRB of Record's Progress Report Form or Application for IRB Review (this document must be signed by either the IRB Chair or the Institutional Official authorized to sign, which shows current dates of approval);
 - Approved version of protocol/activity plan;
 - Approved version of all consent form(s);
 - Approved version of all other materials (i.e. approach letters, questionnaires, etc.).
- d. All IRB Authorization Agreement renewals are to be filed with the IRO within 30 days of the file's expiration. If not, the file will be closed and any *Certifications of Approval* (i.e. *Assurance Identification/IRB Certification/Declaration of Exemption form*, etc.) will not be signed unless the Institutional Review (IR) files are re-activated with a continuation review renewal and show current approval periods.

7. CRR Approval Notification Process

- a. Upon review and determination by the IRB Committee of a *CRR* the PI will be notified in writing of the IRB Committee's determination as outlined in IRB Policy 1.8 *Approval Date Guidelines and Turnaround Times*.
- b. The IRO Staff follows the procedures as outlined below to ensure notification:
 - For *CRRs* which are approved:
 - The IRO staff processes the *CRR* within 24 hours of the IRB meeting following the final processing section of the *CRR Screener Form*.
 - Approval dates are given per the *Approval Dates Guidelines*.
 - The information is entered into the *CRR* tab in the database PIRO.

Copies of the approval documents are forwarded to the contact person and the original documents are filed in the IR file.

- For *CRRs* which are require minor modifications:
 - The IRB Analyst forwards a result letter outlining the minor points of clarification requested by the IRB Committee within a week of the IRB meeting.
 - The PI has five (5) working days from the “approved through date” to return his/her response as well as copies of all modified materials. The IRB may determine that the response can be reviewed by the IRB Chair or designee or subcommittee.
Upon receipt, the response will be screened by the IRB Analyst. If the response is appropriate, the response along with any modified documents and the *CRR* are forwarded to the IRB Chair or designee for review and final approval.
 - If the IRB determines that a subcommittee of the IRB should review the response, the response and any modified documents are forwarded to the subcommittee for review. A subcommittee consists of the primary reviewers of the initial review of the *CRR*. The subcommittee determines whether the response is appropriate and approvable or whether the response requires further full IRB review. The subcommittee cannot disapprove a research activity.
 - For *CRR*'s which are disapproved: If the IRB disapproved the review of a study, the IRB Analyst or IRB Assistant Director on behalf of the IRB Chair or designee, emails the PI/contact person within 24 hours after the meeting to inform them of this determination. The email also informs them that the details of the meeting will be forwarded to them within two (2) business days in the result letter.
- c. The expiration date of the study is determined per *Approval Date Guidelines*.
- d. For *CRRs* undergoing the expedited review process, the IRB Chair or designee will determine that the *CRR* meets one of the expedited review categories.

The IRO staff will complete the following:

- a. *CRR* is processed by the IRO staff per the final processing section of the *CRR Screener Form*.
- Approval dates are given per the *Approval Dates Guidelines*.
- The information is entered into the database PIRO in the *CRR* tab.
- A copy of the approval documents are forwarded to the contact person, a copy of the PDF is placed in the next agenda bin for reporting to the IRB at its next scheduled meeting, and the original documents are filed in their designated IRB file.

8. Failure to Submit Continuing Review Report

If the PI does not submit a *CRR* by the *CRR* submission deadline, the IRB Analyst will contact the PI or contact person as a reminder that the *CRR* is due and requires IRB review and approval to continue the study.

If the PI fails to submit a *CRR* or the IRB has not reviewed and approved a research study by the IRB expiration date, all research must cease. Per IRB Policy 2.9 *Closure and Re-Open*, the IRO staff will initiate closure of the study and will forward the *Closure*

Letter to the PI and contact person informing them the all research activities must cease including recruitment (all medial advertisement must be stopped), enrollment, interventions and interactions, and collection of private identifiable data.

If the PI wishes to continue current research participants/patients in the research because they cannot be treated off protocol or because stopping the research procedures will cause harm, the PI must contact the IRB Chair immediately to provide rationale for the continuation of this treatment/intervention. Funding may be restricted by the Office of Sponsored Research if this is the sole source of research funds, and the FHCRC IRB will not grant the investigator any future protocol approval unless the study receives review by the IRB. No new research participants may be enrolled in the study after the expiration of IRB approval. For additional information regarding the closure or re-opening of studies, please refer to IRB Policy 2.9 *Closure and Re-Open*.

9. The Study is Terminated by the IRB

When study approval is terminated by the IRB, in addition to stopping all research activities, any research participant 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 research participants for safety reasons is permitted or required by the IRB, the research participants should be so informed and any adverse events or outcomes should be reported to the IRB and the sponsor, if appropriate. For detailed information regarding study termination by the IRB, please see *IRB Policy 1.10 Suspension or Termination Initiated by the IRB*.

10. IRO Staff Responsibilities

- a. The IRO Staff follows the instructions outlined in the *IRB Staff CRR Renewal Notice Procedure* to send notification to PI's that a *CRR* is due and track all *CRR*s needed for each research activity approved at FHCRC as noted in step 2.a. of this policy.
- c. The IRO staff utilizes the screeners as appropriate for the research activity to ensure that all information is received in the IRO. Screeners that may be used include:
 - CRR IRB Certification Screener Form
 - CRR Cooperative Screener Form
 - CRR Individual Investigator Agreement Screener Form
 - CRR Authorization Agreement Screener Form
 - CRR Screener Form
 - WSCR Screener Form

If deficiencies are present, the PI or study coordinator is contacted by phone or email, informed of the deficiencies, and if appropriate, the packet will be returned for resubmission with corrections. The file can only be processed once all deficiencies are rectified. Once a packet is complete, the activity is assigned to the appropriate review process (i.e. full or expedited).

- d. The IRO staff will assure that the review of the study is completed by an IRB member (or consultant as needed) that has the scientific or scholarly expertise to review the activity.
- e. The IRO staff documents the findings of the IRB and communicates those findings to the PI and study staff as noted in this policy in Section 5.

SUPPORTING DOCUMENTS

IRB Policy 1.6 Meeting and Meeting Records
IRB Policy 1.8 Approval Date Guidelines and Turnaround Times
IRB Policy 1.10 Suspension or Termination Initiated by the IRB
IRB Policy 2.6 Unanticipated Problems Involving Risks to Subjects and Other
IRB Policy 2.9 Closure and Re-open
IRB Policy 1.9 Noncompliance
Continuation Review Report Form
Principal Investigator Responsibilities Memorandum
IRB Chair Report Checklist
IRB Member Checklist
Closure Letter
CRR IRB Certification Screener Form
CRR Cooperative Screener
CRR Individual Investigator Agreement Screener Form
CRR IRB Authorization Agreement Screener Form
WSCR Screener Form
CRR Screener Form
Expedited Review Checklist for Minimal Risk Activities