FRED HUTCH
Institutional Review Board

Policy/Procedure

Title:	Continuing Review
Policy:	2.2
Version:	10.01
Effective Date:	June 7, 2021
Responsible Office:	Institutional Review Office (IRO)
Responsible Official:	Meghan Scott, IRO Director Digitally signed by Meghan Scott Date: 2021.05.28 16:32:33 -07'00' 5/28/2021
	Signature/date

Version History	Effective Date
10.00	02-24-2020
9.01	05-28-2019
9.00	01-21-2019
8.00	11-20-2017
7.00	07-03-2017
6.02	05-15-2014
6.01	09-01-2012
6.00	01-31-2012
5.04	04-01-2011
5.03	05-17-2010
5.02	05-01-2010
5.01	05-15-2009
5.00	09-26-2008
4.00	01-14-2008
3.00	08-01-2007
2.00	03-13-2007
1.00	12-04-2006

POLICY STATEMENT

It is the policy of Fred Hutchinson Cancer Research Center (Fred Hutch) that the Fred Hutch Institutional Review Board (IRB) will conduct continuing review of most approved human research studies at intervals appropriate to the degree of risk of the study. This review period will never be greater than one year from the previous IRB review date. For research approved under the 2018 Requirements of the Common Rule, continuing review is not required under certain circumstances, unless the IRB determines that continuing review should occur. (Refer to *IRB Policy 2.28 Status Reports for IRB Files* [0403] for details about research that does not require or no longer needs continuing review.) Continuing review will be in accordance with federal regulation, using either an expedited review process or a convened review process. The *Continuing Review Report* (CRR) (045) must contain information to allow the IRB to determine that the research may continue, should be modified, or should be terminated.[1]

DEFINITIONS

See *IRB Glossary of Terms and Acronyms* (050) for full definitions of the following:

2018 Requirements of the Common Rule

Continuing Review

Exempt

Expedited Review

Full Committee Review ***(also known as Full Board Review or fully convened Committee)***

Human Subjects Research

Long-Term Follow-Up

Minimal Risk

Pre-2018 Requirements of the Common Rule

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.

Note: This policy does not apply to research studies that do not require continuing review, including exempt research and research that meets certain conditions under the 2018 Requirements of the Common Rule. (Refer to *IRB Policy 2.28 Status Reports for IRB Files* [0403] for further details.)[2]

INDIVIDUALS AFFECTED BY THIS POLICY

The contents of this policy apply to Institutional Review Office (IRO) staff, IRB members, employees of Fred Hutch, and investigators from other institutions who submit research studies to the Fred Hutch IRB for review and approval.

[1] HHS 2018: 45 CFR 46.109(e)-(f); FDA: 21 CFR 56.109(f)
[2] HHS 2018: 45 CFR 46.109(f)

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.[3]

The IRB may determine that significant new findings regarding the research might affect 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.[4]

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 Continuing Review Report (CRR) must contain the following information:

- 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, including the reason for each withdrawal;
- 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;
- 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, current protocol; and
- any modifications previously approved by the IRB since the last CRR.

2. Continuing Review Report (CRR) Notification Process

a. IRO staff will send each PI conducting research that requires continuing review a *Continuing Review Report Notice* (090, 0290) approximately ten (10) weeks before their current approval expires.

b. Upon receipt of a completed *CRR* (045), 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, current 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 ensure adequate time for review.

[3] HHS 2018: 45 CFR 46.109(d)-(e); FDA: 21 CFR 56.109(e)-(f)

[4] HHS 2018: 45 CFR 46.109(b); FDA: 21 CFR 56.109(b)

New and ongoing studies with NIH funding that undergo continuing review will be evaluated as to applicability of the NIH Certificate of Confidentiality policy. If applicable, the consent form is required to be updated with Certificate of Confidentiality language. See https://grants.nih.gov/grants/guide/notice-files/NOT-OD-17-109.html for NIH policy information. Refer to the model consent templates for language.

NIH-funded clinical trials initiated on or after January 18, 2017, and FDA-regulated applicable clinical trials must be registered with www.clinicaltrials.gov. If the consent form does not already have a statement informing participants of trial registration on clinicaltrials.gov, a statement must be added to the consent form at the time of continuing review.

4. Process for Conducting Continuing Review

a. For continuing review, the IRB reviews the *CRR* as a written progress report from the PI. The *CRR* collects all the relevant information needed by the IRB to determine the IRB approval criteria remain satisfied:
   - Risks to subjects are minimized:
     (i) By using procedures that are consistent with sound research design and that 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 subjects, and the importance of the knowledge that may reasonably be expected to result.
   - Selection of subjects is equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted. The IRB should be particularly cognizant of the special problems of research that involves a category of subjects who are vulnerable to coercion or undue influence, such as children, prisoners, individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons.
   - Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by, §46.116.
   - Informed consent will be appropriately documented or appropriately waived.
   - 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.

b. The IRB reviews a copy of the model consent document currently in use and determines whether the information contained in the consent document remains 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 a review of any unanticipated problems involving risks to subjects or others which may have occurred during the approval period. 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* (032) and *IRB Policy 2.6 Unanticipated Problems Involving Risks to Subjects or Others* (0224).

   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 the list of all such information provided during continuing review, the IRB may reconsider its approval of the study and the frequency for continuing review.

d. The continuing review process is conducted in accordance with federal regulations using either full board review or expedited review (see below):

- Full Board Review at a convened IRB meeting. All IRB members have access to the review materials (submission attachments described in the *CRR*). When an IRB member is not a primary reviewer, they are expected to review the *CRR* and the 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* (071) and *IRB Member Consent Process and Documentation Checklist* (072). Any IRB member may request additional information.

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

- For research studies subject to the pre-2018 Requirements of the Common Rule, an Expedited Review process as allowed by 45 CFR 46.110(a) may be used for the continuing review of research previously approved by the convened IRB as follows:

  Per Category 8 as defined in *OHRP Expedited Review Categories*:

  - 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 *OHRP Expedited Review Categories*, an expedited review process 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 *OHRP Expedited Review Categories* 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 studies reviewed via the expedited review process as noted above, the PI is responsible for submitting the *CRR* and any relevant documents as described the *CRR.*

- For research studies subject to the 2018 Requirements of the Common Rule: Some studies may qualify for the Status Report process instead of Continuing Review. The Status Report process is described in *IRB Policy 2.28 Status Reports for IRB Files* (0403). There are three requirements for utilizing the email-based status report process:

  1. The research is not FDA-regulated; and
  2. The research study was initially approved by the IRB on or after January 21, 2019; and
  3. The research is eligible for expedited review, either because it was determined to be no more than minimal risk by the IRB or because the research study status is currently "closed to accrual, in long-term follow-up only" or "closed to accrual, in data analysis only."

  Note: Even if these three requirements are met, the IRB retains the authority to require Continuing Review and must document this decision with sufficient rationale.[5]

[5] HHS: 45 CFR 46.109(f)(1), 46.115(a)(3)

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

a. The IRB's independent evaluation using *IRB Member Checklist* (071) 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. Information about studies that may require IRB review more often than once a year are included in the *IRB Member Checklist* (071) to assist the IRB Committee or the IRB Chair (or designee) in determining the frequency of review.[6]

   During continuing review, the IRB also considers:

   - Any unanticipated problems involving risks to research participants.
   - Any new information regarding the risks and benefits to the research participants.
   - Risks posed by the study intervention.
   - The type of safety monitoring as provided in the protocol.
   - Changes in the risk/benefit ratio.[7]

b. The IRB will consider whether information from sources other than the PI are needed to verify that no material changes have occurred since the previous IRB review. For example, this may be appropriate if:

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

c. For studies that require continuing review, the IRB may approve the 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 or requiring more frequent reporting to the IRB).[8]

d. Upon review of the *CRR*, the IRB will take one of the actions outlined in *IRB Policy 1.6 Meeting and Meeting Records* (024) if reviewed at the full committee.[9]

e. For *CRR*s undergoing the expedited review process, if 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;
   - Approved with minor modifications;
   - Request full IRB Committee review - The *CRR* does not appear to meet one of the minimal risk expedited review research categories, or there are other concerns. The PI will be notified that the *CRR* requires full IRB Committee review.

f. All *CRR*s which were reviewed under expedited review are reported on the next available committee agenda. IRB members are given an opportunity to request full IRB review or to review additional documents of any items that underwent expedited review.

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[6] HHS 2018: 45 CFR 46.108(a)(3)(ii); FDA: 21 CFR 56.108(a)(2)
[7] HHS 2018: 45 CFR 46.111(a); FDA: 21 CFR 56.111(a)
[8] HHS 2018: 45 CFR 46.109(e); FDA: 21 CFR 56.109(f)
[9] HHS 2018: 45 CFR 46.109(a), 46.110(b)(2); FDA: 21 CFR 56.109(a), 56.110(b)(2)

g. 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 Policy 1.3 IRB Committee Structure* (019) for specific information regarding consultants.

6. Continuing Review Requirements for Participating Sites of a Multi-Site Trial When Fred Hutch Is the IRB of Record

a. When Fred Hutch is the IRB of Record of a multi-site trial, it is the Fred Hutch policy that participating sites will undergo continuing review. The site's continuing review generally will be scheduled for review at the same time as the continuing review for the study. Each site outside the Cancer Consortium is required to submit a separate *Continuing Review Report* (045) (if the site was originally submitted on the *Participating Site Application* [0395]), or else be evaluated on the *Multi-Center Supplement* (0323) (if originally submitted on the *Multi-Center Supplement* [0323]).

7. Continuing Review Requirements When Fred Hutch Is Relying on an External IRB

a. When a Fred Hutch PI is relying on an external IRB of Record, the approval period is that which the external IRB determines. It is the responsibility of the Fred Hutch PI to contact the external IRB's office to become familiar with the necessary continuing review procedure.

b. The Fred Hutch IRO will request annually (or more frequently, if appropriate) that the PI submit copies of the continuing review approval documents. At a minimum, once a year, the Fred Hutch PI is responsible for forwarding the following documents to the Fred Hutch IRO:

- An *External IRB Cover Sheet – Continuing Review or Other* (0321);
- Approved (signed, with current dates of approval) copy of the external IRB's continuing review/status report;
- Current IRB-approved version of the protocol/activity plan (only if modified in the last approval period);
- Current IRB-approved version of the consent form(s) (only if modified in the last approval period);
- Current IRB-approved version of the participant materials (e.g., approach letters, questionnaires, advertisements, etc., only if modified in the last approval period).

c. The PI is responsible for filing all external IRB continuing review documentation with the IRO no later than 30 days after the expiration date. If not, IRO staff will follow up with the study team.

d. For studies that are subject to the 2018 Requirements of the Common Rule and determined to not require continuing review, please see *IRB Policy 2.28 Status Reports for IRB Files* (0403) for further details.

8. CRR Approval Notification Process

a. Upon review of a CRR by the IRB Committee, 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* (06).

b. The IRO Staff follows the procedures as outlined below to ensure notification:

i. For *CRR*s that are approved as submitted:

- The IRO staff processes the *CRR* in accordance with *IRB Turnaround Times* (0411), following the final processing section of the *Screener: Continuing Review Report* (0124).

- Approval dates are given per the *Approval Dates Guidelines* (083).
- The information is entered into the CRR tab in the database PIRO.
- Copies of the approval documents are forwarded to the PI and the IRO Contact, and the original documents are filed in the IR file.

ii. For CRRs that are approved with minor modifications:

- The IRB Analyst forwards a result letter outlining the minor points of clarification requested by the IRB Committee in accordance with *IRB Turnaround Times* (0411).
- The PI must return his/her response as well as copies of all modified materials prior to the expiration date of the study. 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 appears appropriate, the response along with any modified documents and the CRR are forwarded to the IRB Chair or designee for confirmation that all modifications are addressed and for final approval. If the IRB Chair or designee determines the response is not appropriate, it may be referred either to a subcommittee or to the Full Committee for consideration.
- 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 will make recommendations to the IRB Chair or designee and cannot disapprove a research activity.

iii. For CRRs that are disapproved: If the IRB disapproved the review of a study, the IRB staff on behalf of the IRB Chair or designee emails the PI/contact person after the meeting in accordance with *IRB Turnaround Times* (0411) to inform them of this determination. The email also informs them that the details of the review will be forwarded to them in a formal result letter.

c. The expiration date of the study is determined per *Approval Date Guidelines* (083).

d. For *CRR*s undergoing the expedited review process, the IRB Chair or designee will determine that the *CRR* meets one of the expedited review categories.

e. The IRO staff will process the *CRR* per the final processing section of the *Screener: Continuing Review Report* (0124).

i. Approval dates are given per the *Approval Dates Guidelines* (083).

ii. The information is entered into the database PIRO in the CRR tab.

iii. A copy of the approval documents are forwarded to the PI and the IRO Contact, a copy of the first page of the CRR 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 IR file.

9. Failure to Submit Continuing Review Report

If the PI does not submit a *CRR* by the submission deadline, the IRO staff will contact the PI or IRO Contact 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* (08), the IRO staff will initiate closure of the study and will forward the *Closure Letter* (086) to the PI and IRO Contact, informing them that all research activities must cease including recruitment (all media 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 IRO immediately to provide rationale for the continuation of this treatment/intervention. Funding may be restricted by the Office of Sponsored Research. For additional information regarding the closure or re-opening of studies, please refer to *IRB Policy 2.9 Closure and Re-Open* (08).

10. 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 of IRB Approval* (037).

11. IRO Staff Responsibilities

a. The IRO staff emails CRR renewal notifications to PIs and contact person to remind them that a *CRR* is due. The IRO staff tracks all *CRR*s needed for each research activity approved at Fred Hutch as noted in Section 2 of this policy.

b. 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:

Screener: External IRB Cover Sheet – Continuing Review or Other (0127)
Screener: Continuing Review Report (0124)

If deficiencies are present, the PI and IRO Contact are contacted, informed of the deficiencies, and requested to correct and resubmit. Generally, the CRR can only be processed once all deficiencies are rectified. Once a submission is complete, the activity is assigned to the appropriate review process (i.e., full or expedited).

c. The IRO staff will ensure that the review of the study is completed by an IRB member (or consultant as needed) who has the scientific or scholarly expertise to review the activity.

d. The IRO staff documents the findings of the IRB and communicates those findings to the PI and IRO Contact as noted in this policy in Section 5.

SUPPORTING DOCUMENTS

IRB Policy 1.3 IRB Committee Structure (019)
IRB Policy 1.6 Meeting and Meeting Records (024)
IRB Policy 1.8 Approval Date Guidelines and Turnaround Times (06)
IRB Policy 1.10 Suspension or Termination of IRB Approval (037)
IRB Policy 1.11 Reporting Obligations for Principal Investigators (032)
IRB Policy 2.6 Unanticipated Problems Involving Risks to Subjects or Others (0224)
IRB Policy 2.9 Closure and Re-open (08)

IRB Policy 2.28 Status Reports for IRB Files (0403)
Approval Date Guidelines (083)
Closure Letter (086)
Continuing Review Report (045)
Continuing Review Report Renewal Notice for Full Review (090)
External IRB Cover Sheet – Continuing Review or Other (0321)
IRB Authorization Agreement Continuing Review Notification (0290)
IRB Glossary of Terms and Acronyms (050)
IRB Member Checklist (071)
IRB Member Consent Process and Documentation Checklist (072)
IRB Turnaround Times (0411)
Multi-Center Supplement (0323)
Participating Site Application (0395)
Screener: Continuing Review Report (0124)
Screener: External IRB Cover Sheet – CRR or Other (0127)

REFERENCES

All references here to 45 CFR 46 are to the 2018 requirements of the Common Rule.

45 CFR 46.108
45 CFR 46.109
45 CFR 46.110
45 CFR 46.111
21 CFR 56.108
21 CFR 56.109
21 CFR 56.110
21 CFR 56.111
NIH Requirements for Registering & Reporting NIH-Funded Clinical Trials in ClinicalTrials.gov https://grants.nih.gov/policy/clinical-trials/reporting/index.htm
NIH Policy for Issuing Certificates of Confidentiality https://grants.nih.gov/grants/guide/notice-files/NOT-OD-17-109.html
OHRP Continuing Review Guidance: IRB Continuing Review of Research
OHRP Compliance Activities: Common Findings and Guidance #5; #7; #16; #65; #71(a)(b)(c)(e)(g)(k); #72
OHRP Expedited Review Categories
FDA Guidance: IRB Continuing Review after Clinical Investigation Approval
FDA Information Sheets: Frequently Asked Questions: IRB Procedures, IRB Records