



Title:	Modifications to On-Going Activities
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Responsible Office:	Institutional Review Office (IRO)
Responsible Official:	Meghan Scott, IRO Director
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	<i>Signature/date</i>

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POLICY STATEMENT

It is the policy of Fred Hutchinson Cancer Research Center (Fred Hutch) that all proposed changes made to an Institutional Review Board (IRB) approved research study must first receive IRB review and approval prior to implementation of the modification.¹

¹ HHS: 45 CFR 46.108(a)(3)(iii); FDA: 21 CFR 56.108(a)(4)

DEFINITIONS

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

Modification

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.

ALLOWABLE EXCEPTIONS

This policy is meant to be followed without deviation. However, the only exception is a modification that is necessary to eliminate apparent immediate hazards to the research participant. In such a case, after notification of the change, the IRB reviews the change to determine that it is consistent with ensuring the research participants' continued welfare. (Refer to *IRB Policy 2.6 Unanticipated Problems Involving Risks to Subjects or Others* [0224] for reporting requirements.)²

PROCEDURES

Modifications to research include, but are not limited to, changes to IRB-approved study documentation or changes in research participant population, risk information, recruitment, procedures, study design, study sites, principal investigator, or reports to the IRB regarding premature completion of a study or closing of accrual for safety reasons.

Once a study has been fully approved by the IRB, the expectation is that changes in study documentation are submitted to the IRB in a timely manner. When investigators receive updated study documentation from the Sponsor (e.g., revised protocol, updated Investigator Brochure, etc.), these revised documents generally should be submitted to the IRO within 30 days of receipt of the new information, even if the study is closed to accrual. If a study is open to accrual and the revised study documents will not be submitted within 45 days, the PI should submit a Research Modification to change the study status to "Temporarily Closed to Accrual." For changes that could represent an increase in risk to participants, the PI should report this information as soon as possible.

Changes in research personnel, other than the principal investigator, do not require reporting to the IRB unless the change impacts approved study documents, such as the protocol and/or consent form. Such changes to study documents are considered minor and may be incorporated at the time of the next Modification. Note: The Principal Investigator remains responsible to ensure all research personnel continue to meet on-going requirements for training (refer to IRB Policy 2.20, *Training* (038)) and conflict of interest reporting.

Modification review and approval procedures will depend on whether the modifications are minor or major. Federal guidelines allow expedited review procedures for minor modifications, while major modifications require full IRB committee review. The *Research Modification Form* (062) must be attached to all modification requests.

1. Screening Modifications

- a. The IRB Staff follows the *Screener: Modification* (0139) when screening all modifications that are submitted to the IRB.

² HHS: 45 CFR 46.108(a)(3)(iii); FDA: 21 CFR 56.108(a)(4)

- b. When screening the modifications, the IRB Staff will note whether the modification falls under the “major” or “minor” criteria. This information will be provided to the Chair or designee or IRB.

2. Review of Minor Modifications (Expedited Review)

If the research as a whole is minimal risk and was previously determined to qualify for Expedited Review, all modifications generally will be routed through Expedited Review, unless the modification adds procedures that are not allowable in the Expedited Review categories (e.g., adding x-rays, skin biopsies or bone marrow collections).

For research that was determined to be more than minimal risk, minor modifications to the research may be routed for Expedited review by an IRB Chair or designee. A minor change is one which, in the judgment of the IRB Chair or designee, makes no substantial alteration in:

- a. The acceptability of the risk-to-benefit analysis (i.e., the change does not increase the level of risk);
- b. The research design or methods (adding procedures that are not eligible for expedited review would be considered more than a minor change);
- c. The number of subjects to be enrolled in the research as a whole (not just locally);
- d. The qualifications of the research team (i.e., the change does not negatively impact the expertise available to conduct the research);
- e. The facilities available to support safe conduct of the research; or
- f. Any other factor which would warrant review of the proposed changes by the convened IRB.

Minor changes also include the addition of sites to a protocol approved by the convened IRB as long as the investigator(s)/site(s) do not have a conflict of interest, potential compliance concerns (e.g., a 483 that has not been adequately resolved), or any other investigator or site-specific concerns (e.g., qualifications, facilities, or resources to safely conduct the research).

Minor modifications to the research may include and are not limited to the following: reduction in the risk/discomfort to the research participant, changing a funding source document, or making certain wording changes to a consent form that do not substantially alter the meaning or to incorporate IRB-approved language. See section 4 below for additional examples.

Fred Hutch follows the following steps for expedited review of modifications:

- a. The IRB Staff will send the modification to the Chair or designee with a copy of *the IRB Member Checklist (071)* and the *IRB Chair or Designee Review Type Determination form (075)*, which include the required criteria for IRB approval.
- b. The modification will be reviewed by the IRB Chair or designee. If the change affects a regulatory criterion for IRB approval, the IRB Chair or designee will ensure the requirements for IRB approval are met. The IRB Chair or designee will also make the final determination about whether the modification is a “minor” modification approvable by the Expedited procedure. The IRB Chair or designee may not singularly disapprove a modification. They can send the modification to full review if they are not satisfied that the modification meets the expedited review criteria, such as if they determine it is a “major” modification.³
- c. The IRB Staff will follow the *Screener: Modification (0139)* for final processing.

³ HHS: 45 CFR 46.110(b); FDA: 21 CFR 56.110(b)

- d. At the convened IRB meeting, when members are voting on the expedited review and approved items on the agenda, the IRB members may request that an expedited review item receive full committee review or request additional information about the expedited review item.

3. Review of Major Modifications (Full Review)

Fred Hutch follows the following steps for full review:

- a. The IRB Staff places major modifications on the next IRB agenda for full IRB Committee review at a convened meeting. The IRB members will use the *IRB Member Checklist (071)* to assist in the review process. If the change affects a regulatory criterion for IRB approval, the IRB will ensure the requirements for IRB approval are met.
- b. The IRB Staff will follow the *Screener: Modification (0139)* for final processing.
- c. For Modifications 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 by the due date outlined in the letter. 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 Modification 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 generally consists of the primary reviewers of the initial review of the Modification. The subcommittee determines whether the response is appropriate and approvable or whether the response requires further convened IRB review. The subcommittee will make recommendations to the IRB Chair or designee and cannot disapprove a research activity.
- d. For Modifications that are disapproved:
 - IRB staff on behalf of the IRB Chair or designee will email the PI and IRO Contact 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 meeting will be forwarded to them in a formal result letter.

4. Examples of Major and Minor Modifications for Full Review Studies:

<p>Major modifications - Full Review:</p> <ul style="list-style-type: none"> • Increasing the physical or psychological risk/discomfort to the participant or others • The modification requested is in response to an event which involved increased risk to the participant or others • Major change in the design or goal of the study • Adding a new consent form • Expanding the eligibility criteria • Increasing the number of participants at risk • Adding questions about sensitive information (e.g., depression or sexuality) • Adding an element that may breach the confidentiality of the participant (e.g., adding focus groups) • Numerous modifications throughout the year where there may be confusion about the full scope of the study • Whenever a study is closed for safety reasons (e.g., FDA, DSMB, or PI-initiated closures) • Gene Therapy Trial - unless minor administrative changes or the IRB Chair determines that the risk/discomfort is reduced to the participant. 	<p>Minor modifications - Expedited Review routing:</p> <ul style="list-style-type: none"> • Reduction of risk/discomfort to the participant • Adding or removing a Cancer Consortium institution • Changes to recruitment and advertising • Adding a questionnaire or instrument similar to the one already approved (e.g., uses many of the same questions) • Removing question(s) from a questionnaire or instrument • Increasing local accrual (when the total accrual is unchanged) • Minor editorial modifications to the protocol, questionnaire, or consent • Consent form modifications that: <ul style="list-style-type: none"> ○ Add or remove information from the consent form so that it is consistent with an already IRB-approved document ○ Defining a phrase more clearly in lay language ○ Updating a consent form to use IRB-approved template language
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NOTE: The above examples are presented as general guidelines only. Specific modification classifications are made on a case-by-case basis.

5. Review of Study-wide Modifications to Multi-Site Studies:

Study-wide modifications must be approved prior to review of the corresponding modification to a non-Cancer Consortium participating site. In general, modifications to the protocol and other study-wide documents are approved in the master or lead file only. After approval in the lead file, the Fred Hutch investigator may distribute the approved study-wide documents to each participating site that is under the purview of the Fred Hutch IRB.

Modifications to the model consent form are also approved in the lead file first; then additional Modifications must be submitted to incorporate the approved model consent language into each separate site-specific consent form. Generally, the incorporation of IRB-approved model consent form language into the site-specific consent form is considered a minor modification and would therefore qualify for expedited review.

Note: Adding a non-Cancer Consortium participating site is generally considered a minor modification to the study; however, new Non-Cancer Consortium participating sites should submit a *Participating Site Application* (0395), not a *Research Modification Form* (062). See *IRB Policy 2.14 Multi-Center Study Coordination – IRB Review and Oversight* (027) for more information about the review of participating sites.

SUPPORTING DOCUMENTS

- IRB Policy 2.6 Unanticipated Problems Involving Risks to Subjects or Others (0224)
- IRB Policy 2.14 Multi-Center Study Coordination – IRB Review and Oversight (027)
- IRB Chair or Designee Review Type Determination (075)

IRB Glossary of Terms and Acronyms (050)
IRB Member Checklist (071)
Participating Site Application (0395)
Research Modification Form (062)
Screener: Modification (0139)

REFERENCES

21 CFR 56.108
21 CFR 56.110
45 CFR 46.108
45 CFR 46.110
FDA Guidance: Institutional Review Boards and Clinical Investigators Updated September 1998
FDA Guidance: IRB Continuing Review after Clinical Investigation Approval
Food and Drug Administration. Information Sheets: Frequently Asked Questions: IRB Procedures
OHRP Guidance on Written Institutional Review Board (IRB) Procedures
NIH Policy for Issuing Certificates of Confidentiality <https://grants.nih.gov/grants/guide/notice-files/NOT-OD-17-109.html>